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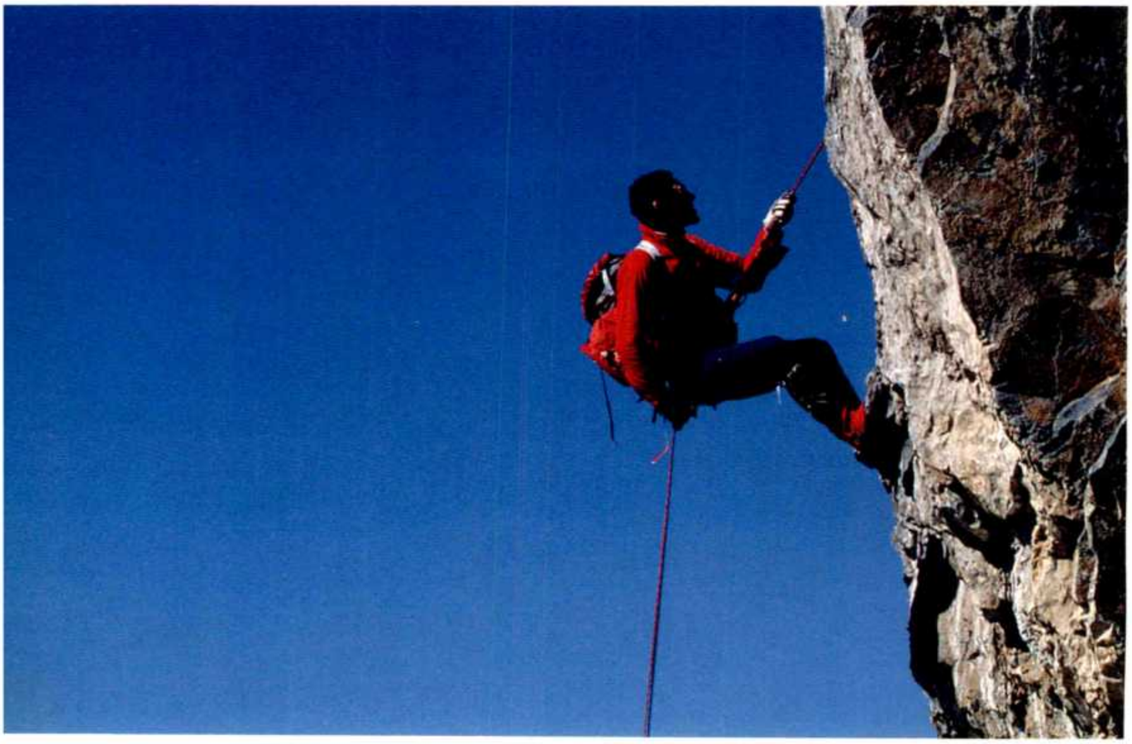

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British Journal of Anaesthesia

OFFICIAL JOURNAL OF
THE COLLEGE OF ANAESTHETISTS

Editor: GRAHAM SMITH

Vol. 67
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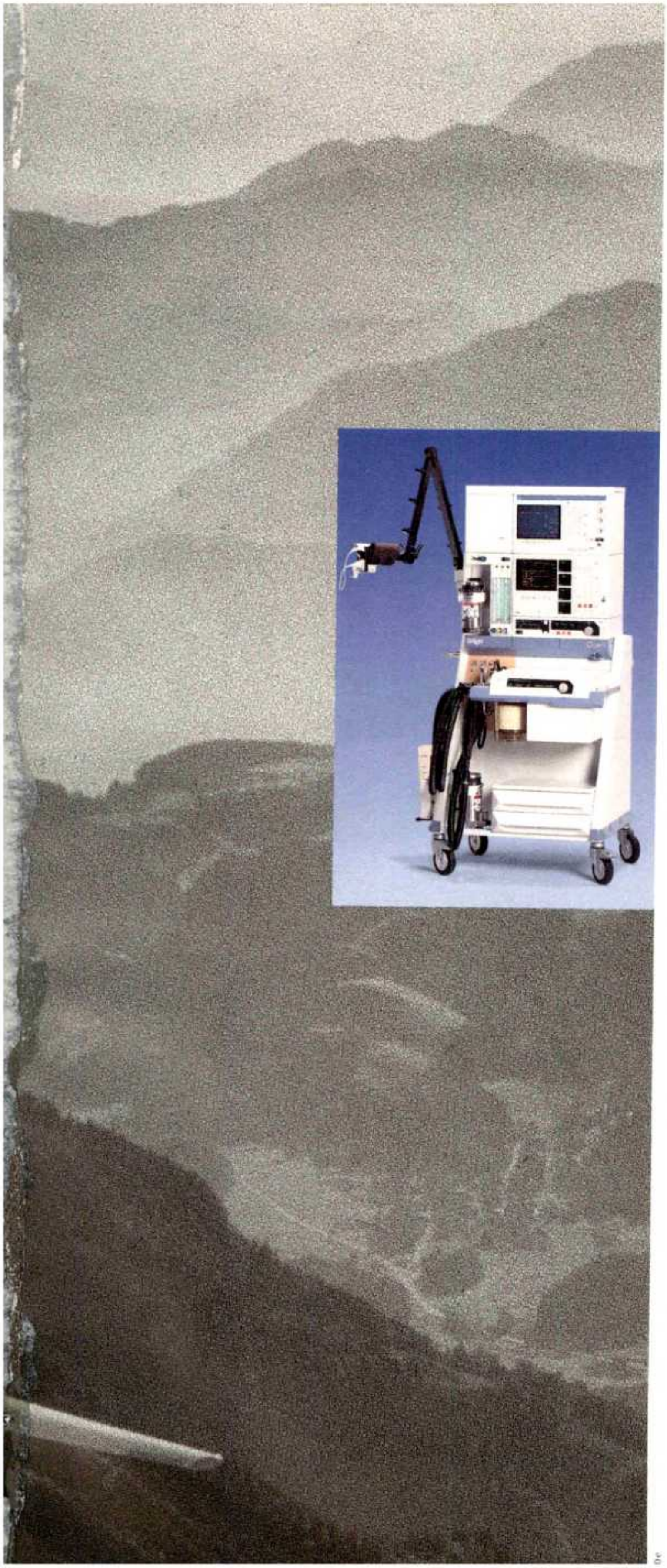

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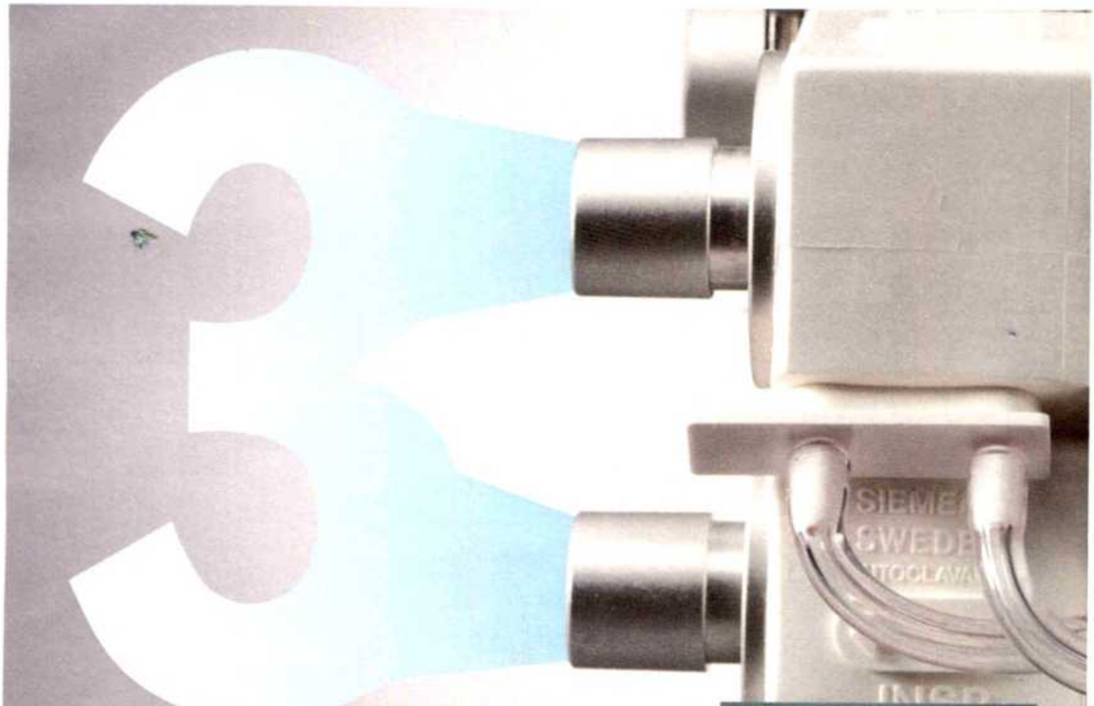

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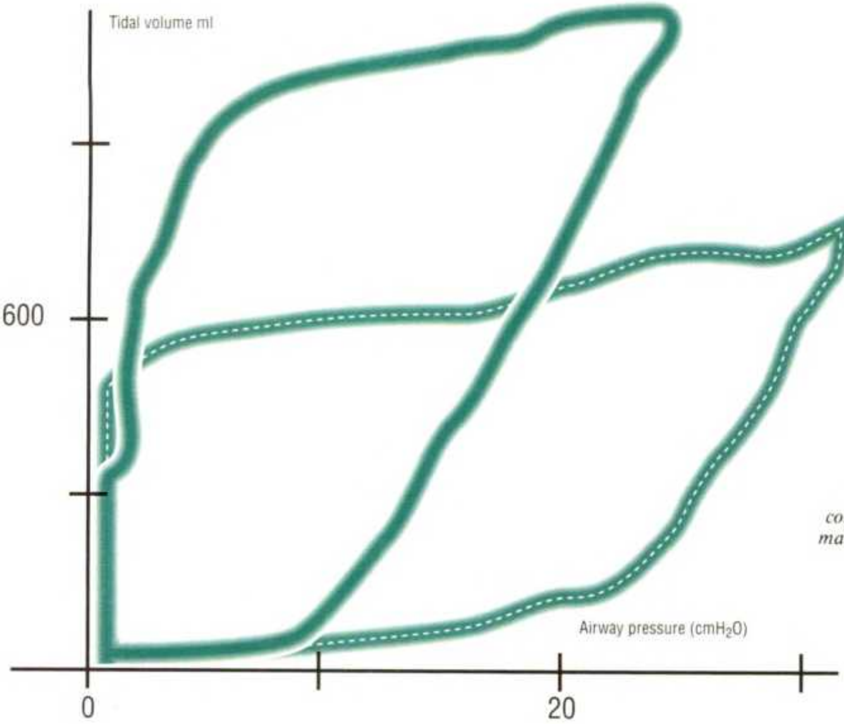

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- Acknowledgements
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The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

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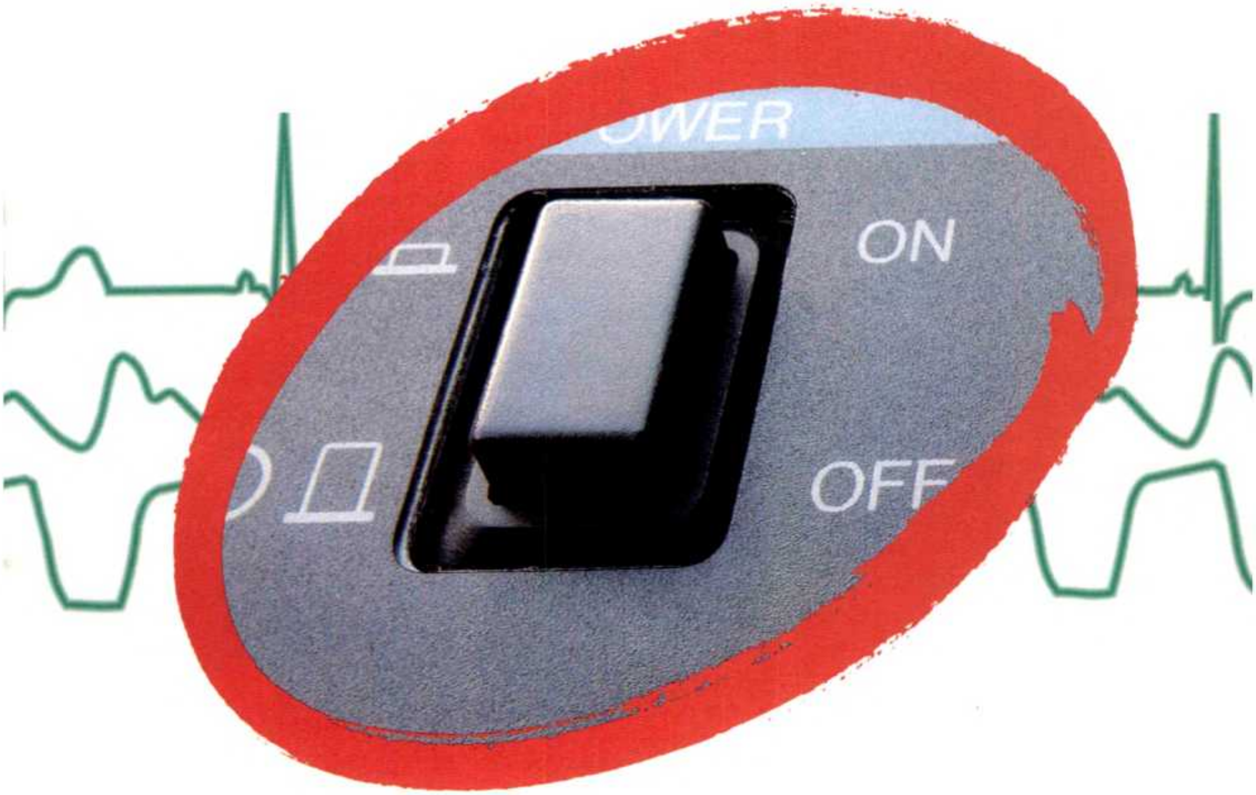

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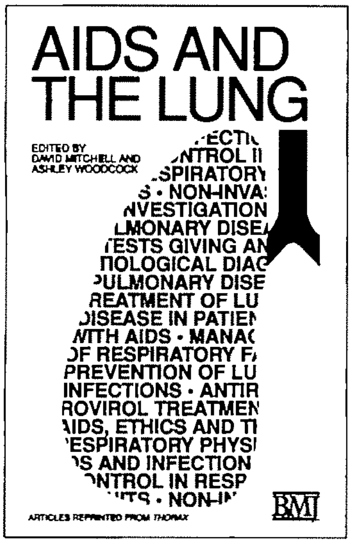
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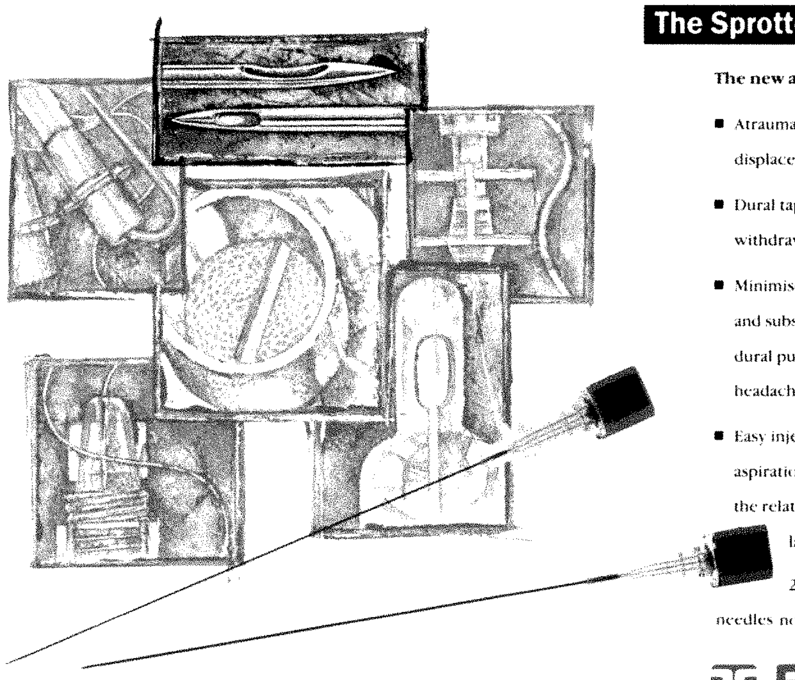

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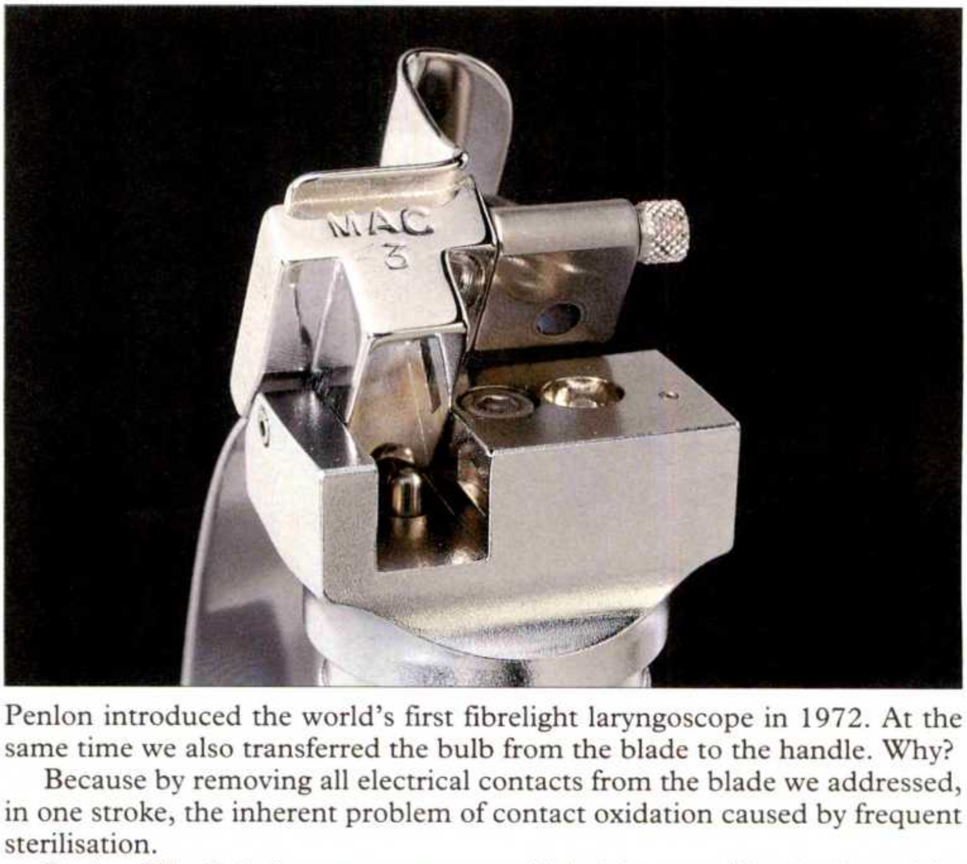

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EDITORIAL

SYNERGISM AMONG I.V. ANAESTHETICS

When two drugs which act on the central nervous system are used in combination in anaesthetic practice, the primary aim is usually to take advantage of the non-hypnotic effects of one or both. Probably the best known example is the use of opioid analgesics in conjunction with i.v. or inhalation anaesthetics. Although pretreatment with an opioid may reduce the induction dose of thiopentone required [1], this is regarded as a secondary effect, the main benefit being from the analgesic and other effects of the opioid. Similar logic underlies the combining of ketamine with midazolam for induction, giving more stable conditions than those seen after the use of each drug alone [2].

However, the recent publication of several studies of the hypnotic effects *per se* of such combinations throws new light on these long established practices. Using loss of ability to open the eyes on command as the end-point for induction of anaesthesia, Tverskoy and colleagues [3, 4] studied the hypnotic effects of combinations of midazolam with thiopentone and methohexitone and demonstrated in each case that the hypnotic effect of the combination was greater than would have been expected from simple summation of the contributions of each component; that is, there was a synergistic interaction between the two agents. In this issue of the Journal, Naguib and Sari-Kouzel [5] report a study in which, using similar methodology, they observed synergism between the hypnotic effects of thiopentone and propofol.

The isobole method, used by all these authors, is the most commonly used technique of analysis of this type of drug interaction [6]. On an isobole diagram, points on the x and y axes, representing the potencies (expressed as the ED_{50} for a particular effect) of each of the two agents used alone, are joined by a straight line which defines the fractional combinations of the two which would be expected to have this same potency if the interaction between them were additive only. If a combination of two agents with a reference point to the left of the line is found to have this potency, synergistic interaction is inferred. In a straightforward additive interaction, the same principle can be expressed in the form

$$\frac{da}{Da}+\frac{db}{Db}=1$$

where Da and Db are the ED_{50} values of agents a and b given alone and da and db are the doses of a and b which, when combined, are equipotent with Da or Db. If the sum of this expression is less than unity, the interaction is synergistic.

The concept that interactions between hypnotic agents might be non-additive derives from studies of the mechanism of anaesthesia. Classical theories of anaesthesia such as the critical volume hypothesis [7] were based mainly on the properties of the chemically heterogeneous group of gaseous and volatile inhalation anaesthetics, particularly the remarkable correlation between their potency and solubility in a lipid environment and the phenomenon of antagonism of anaesthesia by high pressure. In this unitary hypothesis, anaesthesia is envisaged as occurring via expansion of the lipid region by the presence of an inert substance; as a corollary, one anaesthetic may be expected to be replaceable freely by another, and the anaesthetic effect of mixtures may be expected to be strictly additive. This prediction was confirmed experimentally for several combinations of gaseous and volatile agents [8–11].

However, the critical volume hypothesis has clear limitations, notably failure to account for the clinically observed differences between agents, such as the presence or absence of analgesic properties or the variations in cardiorespiratory effects. The hypothesis predicts a linear inverse relationship between anaesthetic potency and pressure, but this relationship was shown to be non-linear for several agents, especially those given i.v. [12]. Richards and White [13] studied in rats the potency of several combinations of i.v. agents using a hypnotic end-point (loss of righting reflex) and found that some combinations, such as that of alphaxalone with etomidate or methohexitone, showed synergism, while others were additive. The University of Alabama group, using similar methodology, found synergism among various combinations of opioid analgesics, benzodiazepines and etomidate [14–17]. These observations, among others, have led to the rejection of the critical volume hypothesis in favour of theories which postulate that anaesthetics act at several different sites, including hydrophobic regions of membrane-embedded protein molecules [12, 18]. Some of these sites, especially in the case of the i.v. agents with their more complex structures, may resemble specific receptor sites. Lipid solubility is thus a necessary, but not a sufficient condition for anaesthesia, and unlike the unitary hypothesis these theories may explain the existence of synergism and antagonism among agents.

Two of the classes of drugs involved in these interaction studies, the benzodiazepines and the opioid analgesics, are known to act via combination with specific receptors, the former on the GABA receptor–chloride channel complex. Barbiturates bind directly to this complex, among several other sites [19], and it is possible that occupation of one site on the complex by a barbiturate molecule might induce a conformational change that would facilitate binding of a benzodiazepine to another site. As the affinities of different barbiturates for the site on the GABA receptor do not correlate with their anaesthetic potency [20], the main site of action of barbiturates is presumably elsewhere. There is thus the possibility that two or more barbiturate effects (one in conjunction with a benzodiazepine) combine, and this would explain the appearance of synergism.

The mechanism of action of propofol is not known at present, but the findings of Naguib and Sari-Kouzel [5] may be explained on the basis of a similar type of interaction. However, the synergistic effects described in all these studies could also be caused by pharmacokinetic, as opposed to pharmacodynamic factors. The former must be regarded as a strong possibility, as these agents are highly protein bound, with scope for competition for binding sites, and have profound cardiovascular effects such that one might influence the volume of distribution of the other. Kissin and colleagues [17] found that brain concentrations of morphine and diazepam in rats were not affected each by the presence of the other, and concluded that the synergistic interaction was unlikely to be on a pharmacokinetic basis. Unpublished work from the Queen's University Department of Anaesthetics, Belfast, suggests that there is no *in vitro* competition for protein binding sites between midazolam and propofol, despite the occurrence in patients of a synergistic interaction between them [S. McClune, 1990, personal communication].

Are these findings of any clinical value? This depends largely on whether or not the cardiorespiratory and other non-hypnotic effects also show synergism. If the interaction is pharmacokinetic, there must obviously be important synergistic effects, but if not, it is possible that there may be different types of interaction between different properties. It has been thought for many years that thiopentone has an antanalgesic action in man [21]. Kissin and colleagues [16, 22] found in rats that, while opioids and thiopentone are synergistic in their hypnotic effects, they are mutually antagonistic to an analgesic end-point, the tail clamp reflex. These laboratory observations need to be re-examined in suitably designed clinical studies.

If there is any clinical benefit obtainable from synergistic combinations in anaesthetic practice, it should be most evident in i.v. infusion techniques. Studies of these techniques should be designed to investigate if measurable advantages, such as shortened recovery times, may be obtained.

A. C. McKay

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THIOPENTONE–PROPOFOL HYPNOTIC SYNERGISM IN PATIENTS

M. NAGUIB AND A. SARI-KOUZEL

SUMMARY

The hypnotic effects of thiopentone, propofol and their combination were studied in 120 unpremedicated ASA group I patients. The end-point for induction of anaesthesia was taken as inability to open the eyes to command 60 s after the end of injection. The dose–response curves were determined by probit analysis. Isobolographic and algebraic (fractional) analyses were used to assess quantitatively the combined hypnotic effect of thiopentone and propofol and to define the type of interaction between these two drugs. The interaction between thiopentone and propofol was found to be synergistic.

KEY WORDS

Anaesthetics, intravenous thiopentone, propofol. Interactions (drug) thiopentone, propofol. Potency: ED_{50}

Propofol represents a new class of i.v. anaesthetic agents, which is unrelated chemically to the barbiturates, steroid or eugenol agents.

Barbiturates are thought to exert many of their effects via enhancement of gamma-aminobutyric acid (GABA)-mediated inhibition in the central nervous system [1, 2]. Components of the GABA receptor–ionophore complex include the GABA receptor, chloride ion channel, benzodiazepine binding site and barbiturate–picrotoxin–meprobamate binding site [3]. Barbiturates increase chloride ion flux through the channel, and thereby cause hyperpolarization of the postsynaptic membrane, inhibiting conductance [1–3]. In addition, there is evidence that barbiturates may interact directly with the chloride channel [4]. Propofol probably acts by modulation of GABA neurotransmission, although the exact mechanism is unknown [1].

A combination of agents with effects greater than expected from its constituents is said to show synergism. A combination with actions less effective than expected is said to show antagonism, and one no more and no less effective than expected is said to show additive effects. Synergy and antagonism imply that the constituents affect each other's action—that is, they interact pharmacologically [5].

This study was designed to quantify the combined hypnotic effect of thiopentone and propofol and to define the type of interaction between the two drugs.

PATIENTS AND METHODS

After obtaining institutional approval and informed consent, we studied 120 ASA group I unpremedicated patients aged 20–45 yr admitted for minor surgical procedures. Patients who had taken benzodiazepines, opioid drugs or other sedative agents within 1 month of the investigation were excluded. Three groups were studied: one group received thiopentone, the two others received either propofol or a thiopentone–propofol combination. The following predetermined doses of drugs were administered to subgroups of six patients: thiopentone 2, 2.5, 3, 4, 4.5, 5, 5.5, 6 mg kg^{-1}; propofol 1, 1.2, 1.5, 1.7, 2, 2.25, 2.4 mg kg^{-1}; thiopentone and propofol, respectively, 0.86 and 0.3, 0.86 and 0.6, 0.86 and 0.8, 0.86 and 0.9, 0.86 and 1.1 mg kg^{-1}. Patients were assigned at random to the subgroups and stratified sampling was used to obtain an even sex distribution. Studies of the single-drug groups were

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This article is accompanied by an Editorial.

MOHAMED NAGUIB, M.B., B.CH, M.SC, F.F.A.R.C.S.I., M.D.; ASAAD SARI-KOUZEL*, M.B., B.CH., D.A., F.F.A.R.C.S.I.; Department of Critical Care Medicine, Faculty of Medicine and Health Sciences, United Arab Emirates University, P.O. Box 17666, Al Ain, United Arab Emirates. Accepted for Publication: January 30, 1991.

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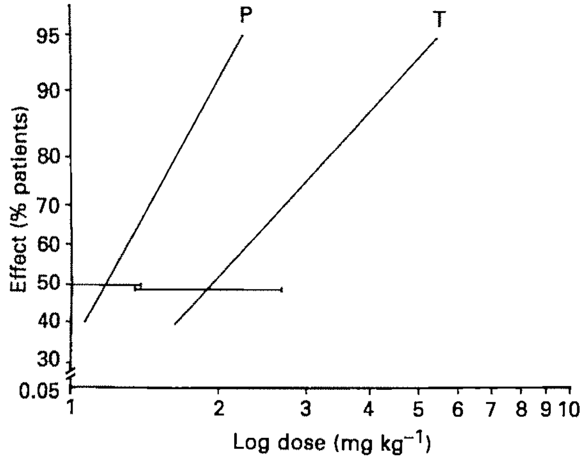

FIG. 1. Thiopentone (T) and propofol (P) quantal dose–response curves. The horizontal lines at the ED_{50} level indicate 95% confidence limits.

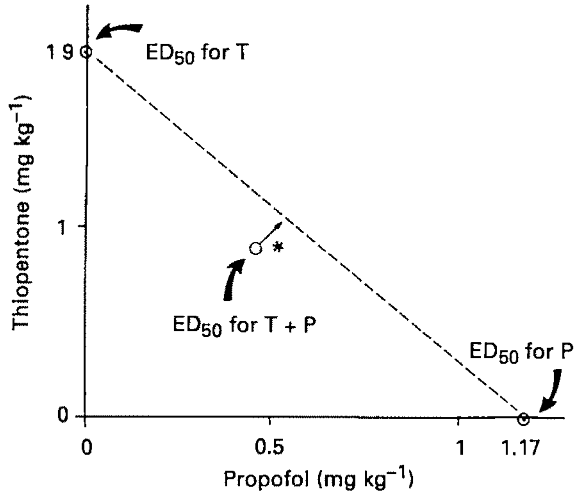

FIG. 2. ED_{50} isobologram for the interaction of thiopentone and propofol assessed by loss of response to verbal command 60 s after induction of anaesthesia. ED_{50} values indicate the dose that provides the effects in 50% of patients when each drug is used alone. The straight line connecting the single-drug ED_{50} points is the additive line. $*P < 0.05$ (level of statistical significance for deviation of the combined ED_{50} point from the additive line).

concluded first, so that doses for the combination could be planned.

All drugs were injected in 15 s into a rapidly flowing i.v. infusion. In the combination group, drugs were injected simultaneously into two separate i.v. catheters inserted in one arm. An investigator, unaware of which drug had been injected, assessed the patient's level of consciousness. Abolition of the ability to open the eyes on command, 60 s after the end of injection, was used as an end-point of anaesthesia.

Dose–response curves and ED_{50} values were determined by fitting the number of patients unable to respond to the command at each dose to a probit model [6] using PCNONLIN [7]. Isobolographic [8, 9] and algebraic (fractional) [5] analyses were used (ED_{50} level) to define the type of interaction between thiopentone and propofol. With isobolographic analysis, ED_{50} values from all groups of patients were plotted in the form of an isobol. Single-drug ED_{50} points were placed on the dose co-ordinates of the isobologram, and a combined ED_{50} point in the dose field. A straight line joining the single-drug ED_{50} points is termed the "additive line" and the deviation of the ED_{50} of a combination to the left indicates synergism. The deviation of a combined ED_{50} point from the additive line was measured as the length along a line running from the point in question to the additive line perpendicular to it. The SE of this distance was computed by the method of propagation of error [10], and error estimates from a combined ED_{50} point and single-drug ED_{50} points were used. An approximate t test used to test the assumption of additivity was obtained as the ratio of the measured distance to its standard error [11].

Algebraic (fractional) analysis was based on the expression of the component doses of thiopentone and propofol of the combination (Tc and Pc) as fractions of the doses that produce the same effect when given separately (Tc/Ts and Pc/Ps). The sum of fractional doses equals to 1.0 in summation, as expressed by the following equation;

$$Tc/Ts + Pc/Ps = 1.0$$

In synergism, the sum of fractional doses is less than 1.0, and in antagonism it is greater than 1.0.

RESULTS

The groups were comparable with respect to age and weight. The calculated ED_{50} values for thiopentone and propofol were 1.9 mg kg^{-1} (95% confidence limits, 1.3–2.7 mg kg^{-1}) and 1.17 mg kg^{-1} (95% confidence limits, 0.9–1.4 mg kg^{-1}) respectively. Comparison of the thiopentone and propofol dose–response curves showed that the difference between slopes was not statistically significant (the 95% confidence limits overlapped) (fig. 1).

TABLE I. *Thiopentone–propofol hypnotic interaction: equi-effective doses (ED_{50}) of thiopentone–propofol combination*

Group	Thiopentone component Fraction of ED_{50}	 Dose ($mg\ kg^{-1}$)	Propofol component Fraction of ED_{50}	 Dose ($mg\ kg^{-1}$)	Sum of fractions
Thiopentone	1.00	1.9	—	—	1.0
Propofol	—	—	1.00	1.17	1.0
Thiopentone–propofol	0.45	0.86	0.39	0.46	0.84

On the thiopentone–propofol isobologram for ED_{50} doses, the combined ED_{50} point deviated to the left ($P < 0.05$) from the additive line, indicating synergism (fig. 2) The fractional (algebraic) analysis of this interaction also demonstrated synergism by virtue of the smaller fractional dose needed for the same effect with combined administration (table I).

DISCUSSION

The ED_{50} value of 1.9 $mg\ kg^{-1}$ for thiopentone found in this study is close to the ED_{50} value for thiopentone (2.2 $mg\ kg^{-1}$) reported by Stella, Torri and Gastiglioni [12] in premedicated patients, and that reported by Tverskoy and colleagues [13] in unpremedicated patients (2.9 $mg\ kg^{-1}$). In the latter study, the response to verbal command was assessed 2 min after injection of thiopentone. Grounds, Moore and Morgan [14], using a different methodology, reported that the ED_{50} for propofol was 1.6 $mg\ kg^{-1}$ and the potency of propofol to thiopentone was 1:1.604. These values are in agreement with our results.

We calculated the ED_{50} for thiopentone and propofol at 60 s after injection because Cote and colleagues [15] demonstrated a variability in response 30 s after injection of thiopentone, while the response at 60 s was more constant.

Isobolographic and algebraic analyses used in this study demonstrated a synergistic thiopentone–propofol interaction in relation to the hypnotic effect. The combination of the two drugs gave an ED_{50} which was 0.84 of the fractional dose needed for ED_{50} for each drug when given alone. The synergistic interaction between thiopentone and propofol may be explained on the basis of interaction at the GABA receptor complex.

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NITROUS OXIDE SEDATION CAUSES POST-HYPERVENTILATION APNOEA†

D. NORTHWOOD, D. J. SAPSFORD, J. G. JONES, D. GRIFFITHS AND C. WILKINS

SUMMARY

We have studied, in six normal subjects, the effect of nitrous oxide sedation on the ventilatory pattern and oxygen saturation using pulse oximetry (Sp_{O_2}) after hyperventilation to an end-tidal carbon dioxide partial pressure (PE'_{CO_2}) of 3 kPa. This value of PE'_{CO_2} was shown to be less than the apnoeic threshold of all these subjects when their ventilation vs PE'_{CO_2} response curves were plotted. All subjects became apnoeic when told to relax following hyperventilation while breathing 75% nitrous oxide for 90 s. Apnoea was defined as cessation of breathing for 20 s or more. The mean duration of apnoea was 78 s (range 29–130 s). All subjects demonstrated arterial desaturation (mean Sp_{O_2} 75%, range 44–87%). In contrast, following hyperventilation with air, no apnoea was seen in any subject, although there was some evidence of desaturation (mean Sp_{O_2} 92.5%, range 88–98%). It was concluded that subjects who are sedated with nitrous oxide behave similarly to those who are anaesthetized rather than to those who were fully conscious, in that they become apnoeic below the apnoeic threshold point. The reduction in Sp_{O_2} after hyperventilation was explained almost entirely by apnoea and may explain abnormalities of respiratory control and hypoxaemia in patients recovering from general anaesthesia or sedation accompanied by hypocapnia. This mechanism may be of importance in obstetric patients after breathing Entonox, when apnoea and hypoxaemia may reduce oxygen delivery to the fetus.

KEY WORDS

Anaesthetics, gases: nitrous oxide sedation. Carbon dioxide: apnoeic threshold, hypocapnia. Measurement techniques: pulse oximetry. Ventilation: hypoventilation, pattern.

Previous work has demonstrated a reduction in arterial oxygen saturation (Sa_{O_2}) in normal subjects after hyperventilation with Entonox (50% nitrous oxide: 50% oxygen) which was greater than that seen after hyperventilation with 50% oxygen in nitrogen [1]. Suggested mechanisms for this include an effect of nitrous oxide on the ventilatory response to carbon dioxide, the ventilatory response to hypoxia, ventilation/perfusion matching and diffusion hypoxia. It is well known that spontaneously breathing but anaesthetized patients become apnoeic if they undergo hyperventilation to a Pa_{CO_2} less than their apnoeic threshold [2]. In contrast, naive awake subjects continue to breathe if they first voluntarily hyperventilate to a Pa_{CO_2} less than the apnoeic threshold and then relax. It is unknown if patients who are *sedated* with nitrous oxide or other drugs behave as anaesthetized or awake patients. We have investigated, therefore, the possibility that nitrous oxide sedation produced by a brief period breathing nitrous oxide affects ventilatory control when a subject is breathing at an end-tidal carbon dioxide (PE'_{CO_2}) less than the apnoeic threshold so as to produce both apnoea and hypoxaemia.

SUBJECTS AND METHODS

Six normal healthy volunteers gave informed consent to the study, which was approved by the hospital Ethics Committee. The study was des-

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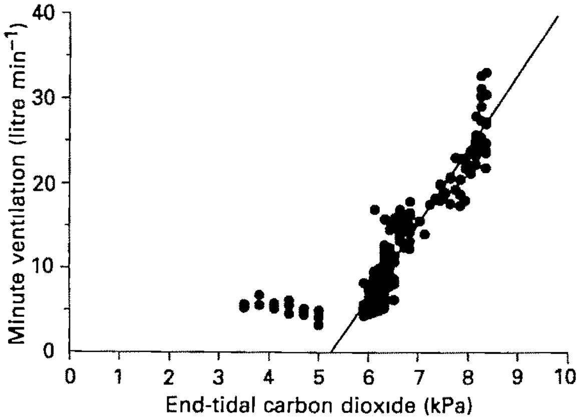

FIG. 1. Quasi steady state carbon dioxide response curve of one subject. Regression line is extrapolated to the X-axis, showing an apnoeic threshold of 5.25 kPa. Note the continuation of ventilation after hyperventilation to a $P\text{E}'_{CO_2}$ of 3.5 kPa.

cribed to each subject, but they were not told that apnoea was expected after hyperventilation.

There were three parts to the study: carbon dioxide response curve obtained using a quasi steady state method; hyperventilation with air immediately followed by nitrous oxide; hyperventilation breathing room air. The three parts of the study were obtained in a random fashion on different days.

Subjects were familiarized with the equipment and told that they should comply with orders given during the study periods. These commands would be to commence hyperventilation, to stop hyperventilating and relax completely, or to take a deep breath.

Equipment

The subject was asked to breathe through a mouthpiece whilst wearing a nose-clip. A Fleisch II pneumotachograph was connected to the mouthpiece which led in turn to a low resistance T-piece with one-way valves. The expiratory limb was open to atmosphere and the inspiratory limb was connected to a three-way tap. This allowed delivery of inspired gas to be changed from room air to that held in a 70-litre Douglas bag, which contained a mixture of 75% nitrous oxide in oxygen. The Douglas bag and three-way tap were situated behind the subject. All tubing, including the tap, was low resistance, wide bore. Subjects could not distinguish between inspired gas coming from atmosphere or from the bag. An Ohmeda 6000 multi-gas mass spectrometer, calibrated and used according to the manufacturers' instructions, was used to check the composition of the mixture. The mass spectrometer was used also to sample inspired and end-tidal oxygen, nitrogen, carbon dioxide and nitrous oxide from the mouthpiece. A Validyne CD12 carrier demodulator was used to process the pneumotachograph signal and the output was relayed to a computerized data acquisition system. This enabled tidal volume, ventilatory frequency, inspired and expired times, inspired and expired minute volume and breath number to be measured throughout the study period. An Ohmeda Biox 3700 pulse oximeter was used to monitor arterial oxygen saturation (Sp_{O_2}). All variables monitored were stored on hard disc and displayed contemporaneously by the computer. A copy was obtained on paper using a Brother M-1709 printer.

Carbon dioxide response curves

The breathing system was modified for this part of the study by connecting the pneumotachograph to a Magill circuit fitted with a 6-litre bag. A Boyle anaesthetic machine was used to supply oxygen to the circuit and carbon dioxide was introduced in a stepwise fashion by increasing the flow in 100-ml min^{-1} increments to increase $P\text{E}'_{CO_2}$. Three or four increments were used to generate each curve, each increment taking 4 min.

The same measurements of inspired and expired gas tensions, respiratory variables and Sp_{O_2} were sampled by the computer and stored as before.

Hyperventilation studies

The subject was allowed time to become accustomed to breathing through the apparatus. When $P\text{E}'_{CO_2}$ and minute volume were constant, the subject was told to hyperventilate. Large tidal volumes were preferred to rapid rates. When $P\text{E}'_{CO_2}$ 3 kPa was reached, that minute volume was maintained for 2 min. $P\text{E}'_{CO_2}$ was maintained close to 3 kPa, the subject either increasing or decreasing ventilation appropriately at the command of the observer. At this point, the hyperventilation was continued for a further 90 s with the subject breathing either room air or the 75% nitrous oxide in oxygen mixture.

When this period was complete, the subject was instructed to relax and breathe quietly, the inspired gas being changed to room air if nitrous oxide had been given during hyperventilation.

TABLE I. *Duration of apnoea and least Sp_{O_2} in each subject after hyperventilation with air or 75% nitrous oxide.* *$P < 0.05$ *compared with air (Wilcoxon signed rank test)*

	Duration of apnoea (s)		Least Sp_{O_2} (%)	
Subject	Air	N_2O	Air	N_2O
1	—	29	94	81
2	—	130	98	44
3	—	70	88	87
4	—	30	93	77
5	—	120	94	75
6	—	90	88	86
Mean (SD)	—	78 (43)	92.5 (3.9)	75 (15.9)*

The study finished when PE'_{CO_2}, minute ventilation and Sp_{O_2} returned to near normal values. These variables were monitored continuously during the acclimatization period. During the relaxation stage the subject was not disturbed unless Sp_{O_2} decreased to less than 85%, when they were asked to take a single deep breath.

RESULTS

Five males and one female (ages 26–54 yr) took part in the study.

Carbon dioxide response curves

Plots of minute ventilation against PE'_{CO_2} demonstrated a linear relationship, so that a regression line was calculated and the intercept with the X-axis was plotted to give the apnoeic threshold (fig. 1).

The mean apnoeic threshold for the six subjects was 5.3 (SD 0.3) kPa (range 4.9–5.4 kPa). Minute ventilation was measured also in each subject after a short period of hyperventilation with air. These values were plotted on the carbon dioxide response curves, producing a "hockey stick" shape to the plot in every subject.

Hyperventilation with nitrous oxide

The inspired mixture was 75% nitrous oxide and 4% nitrogen in oxygen. Subjects breathing nitrous oxide were able to respond to verbal commands given by the observer, although there was impairment of normal cognitive function in all subjects and they later reported a variable period of amnesia which started at the latter stages of breathing nitrous oxide. After hyperventilation, all of the subjects became apnoeic, defined as the cessation of breathing for 20 s or more (table I). Three subjects needed prompting to take deep breaths because of the onset of hypoxaemia (Sp_{O_2} < 85%). One did not respond immediately to the command to take a breath but removed the mouthpiece and nose-clip, when further prompting restored spontaneous ventilation. The period of apnoea sustained by this subject was 130 s; this was included in the results table.

Plots of minute ventilation and Sp_{O_2} against time (fig. 2) show that arterial desaturation corresponded to periods of hypoventilation which included apnoea. The mean value of the least saturation noted following nitrous oxide breathing was 75 (15.9)% and occurred at the end of apnoea (table I).

The mean PE'_{CO_2} noted when spontaneous ventilation returned was 4.4 (0.4) kPa.

Hyperventilation with air

Although minute ventilation was reduced after hyperventilation, no periods of apnoea were noted.

The decrease in minute ventilation in the 3-min period after hyperventilation with air and nitrous oxide may be seen in figure 3. The presence of nitrous oxide clearly depressed minute ventilation and the values in the first 60 s represent virtual apnoea. The mean reductions in minute ventilation after air or nitrous oxide were significantly different ($P < 0.05$, paired t test).

Sp_{O_2} also decreased during the period after hyperventilation. The mean of the smallest values was 92.5 (3.9)%. This was significantly different from the value of 75% obtained after exposure to nitrous oxide ($P < 0.05$, Wilcoxon signed rank test) (table I).

DISCUSSION

During measurements for the carbon dioxide response curves, ventilation increased in a linear manner with increasing concentrations of inspired

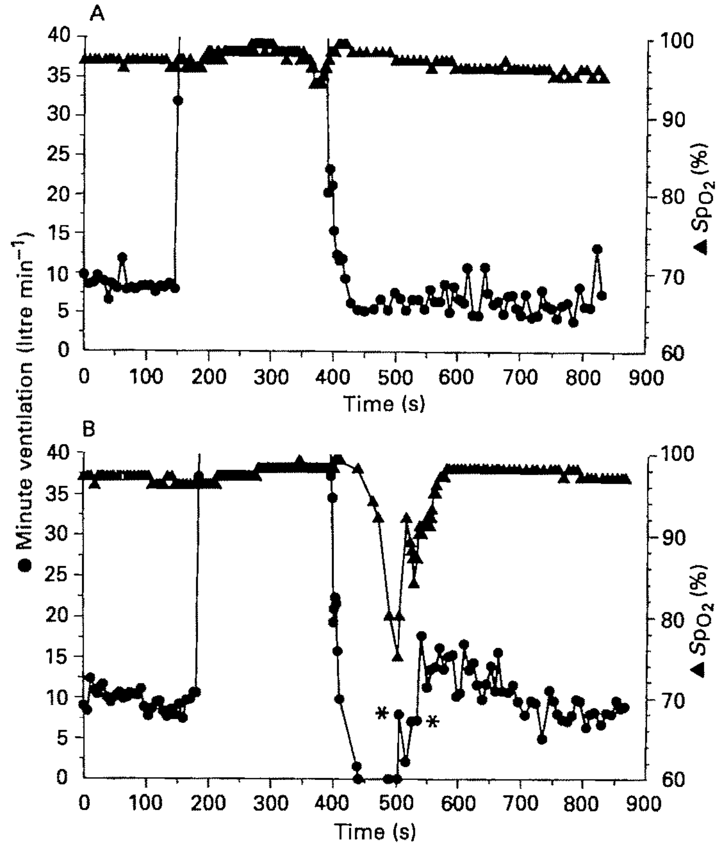

FIG. 2. Plots of minute ventilation (●) and arterial oxygen saturation (▲) against time. Curves show initial acclimatization period, hyperventilation and then relaxation: A following hyperventilation with air; B following hyperventilation first with air then for 90 s with nitrous oxide. *Forced breath.

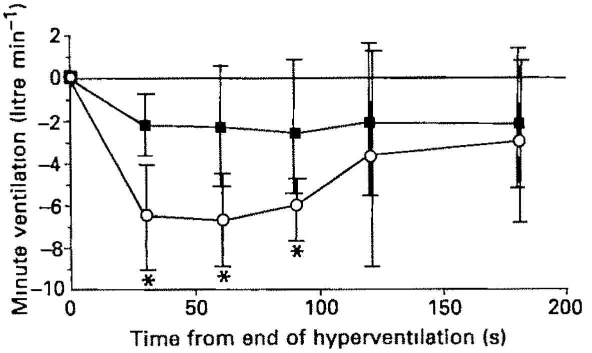

FIG. 3. Change in minute ventilation against time immediately after a period of hyperventilation with air (■) and with nitrous oxide (○). Bars represent 95% confidence limits. *$P < 0.05$ (paired Student's t test).

carbon dioxide over a wide range. Severe hypercapnia is reported to depress ventilation, but this extreme was avoided in this study and extrapolation of the curve to the abscissa indicates a concentration of carbon dioxide at which ventilation should become zero—the apnoeic threshold. This, of course, assumes that the $\dot{V}\text{E}$ against $P\text{E}'_{\text{CO}_2}$ response is linear at values less than the normal $P\text{E}'_{\text{CO}_2}$.

In the anaesthetized, spontaneously breathing subject, ventilation is studied easily and there is no doubt that hyperventilation to less than the apnoeic threshold induces apnoea in this state [2]. Inducing hypocapnia in awake human subjects and obtaining this threshold experimentally has proved difficult and conflicting results have been reported in the literature. For example, in the awake state hyperventilation was reported to be followed by apnoea [3], a normal ventilatory pattern [4] or hyperventilation [5]. Other studies have experienced all these various responses in their study groups [6, 7]. Some of the work has been criticized because preconceived ideas by the subjects participating in the study could have influenced the results [8]. Study designs have differed also, especially the degree of hypocapnia reached and the duration for which it was maintained. In Bainton and Mitchell's study [7], three of 16 awake subjects demonstrated apnoea after hyperventilation on the first occasion they were studied, but they reported that 15 of 16 became apnoeic after further trials. However, their definition of apnoea included a "missed breath" and although this period of apnoea was lengthened—by repeating the study on successive days—only three subjects demonstrated apnoea by our criteria.

The results from all the subjects in our study showed no apnoeic periods following hyperventilation with air and all our subjects continued breathing at hypocapnia, which supports the concept of the "hockey stick shaped" carbon dioxide response curve (fig. 1). Nielsen and Smith [9] demonstrated this first with hypoxic hypocapnic breathing, and it suggests that there is a threshold above which carbon dioxide concentration must increase before ventilation is stimulated. Fink [8] has proposed that a "wakefulness stimulus" maintains ventilation below this threshold, but the important transition zone between anaesthesia and normal consciousness has not been investigated. Our results showed that sedation induced by a brief period of hyperventilation with nitrous oxide caused apnoea when the $P\text{E}'_{CO_2}$ was less than the apnoeic threshold. At first sight, it is surprising that the mean $P\text{E}'_{CO_2}$ value on return of spontaneous breathing following apnoea was 4.4 kPa, which is 0.9 kPa less than our mean measured apnoeic threshold. This could be a result of the appearance of the respiratory stimulant effects of nitrous oxide as it was being eliminated [10]. Alternatively, our estimate of the apnoeic threshold may have been too great because of a shift in the response curve to the right. This may occur using a dynamic method of measurement of the carbon dioxide response (a quasi static method), as a lag in the ventilatory response occurs as a result of circulatory times and the state of the central chemoreceptors and respiratory centres. Carbon dioxide partial pressures here may have been initially smaller than normal at the start of the assessment because of a tendency shown by subjects to increase their minute ventilation when breathing via a mouthpiece and nose-clip [11, 12]. Thus a mild carbon dioxide depletion would have occurred during the acclimatization period and restoration of carbon dioxide concentrations in the respiratory centres may have moved the curve to the left again.

It is interesting to note that, at the eucapnic region of the curve, a decreased ventilatory sensitivity to a low inspired concentration of carbon dioxide has been reported [13]. This may imply that the response curve may have two "dog legs" in its course not one, and the apnoeic threshold obtained by extrapolation would move again to the left. Nunn [14] has proposed a shift of 0.7 kPa in the carbon dioxide response curve if the discrepancy between the $P\text{E}'_{CO_2}$ at the return of spontaneous ventilation and that at the apnoeic threshold is a result of measurement by dynamic methods. This correction would make our mean apnoeic threshold 4.5 kPa, which is close to the mean $P\text{E}'_{CO_2}$ at the return of spontaneous breathing.

A reduction in Sp_{O_2} occurred in the period after hyperventilation in almost all subjects. This occurred after air or nitrous oxide breathing, but was most profound after apnoeic periods which occurred only after exposure to nitrous oxide. Although end-tidal oxygen was undoubtedly diluted by the washout of nitrous oxide, its contribution to the production of hypoxaemia has been shown to be very small in normal healthy subjects [15–17]. It is conceivable that, during the period of apnoea, there is no net transfer of nitrous oxide from blood to alveoli, without ventilation to provide a washout gradient. The degree of oxygen desaturation reached by each individual during apnoea is a function of metabolic rate and FRC, which acts as a reservoir of oxygen. Without knowing these two variables, it is not possible to predict accurately the degree of desaturation to expect following a period of apnoea. However, if it is assumed that FRC is 2 litre and oxygen consumption is 200 ml min^{-1}, it can be calculated that during apnoea the Sp_{O_2} would decrease to about 80% after 80 s. Our result, a mean Sp_{O_2} of 75% with a mean duration of apnoea of 78 s, is consistent with this prediction and suggests that apnoea is the predominant cause of the hypoxaemia noted in this study.

In conclusion, we have shown that the reduction of $P\text{E}'_{CO_2}$ to less than the apnoeic threshold in normal subjects in the presence of nitrous oxide-induced sedation causes apnoea and hypoxaemia. The influence of other forms of sedation and that of drowsiness or sleep remains to be investigated further. It is worthy of note that Fink reported two of his subjects "dozed off" whilst hypocapnic and immediately became apnoeic [4]. Spontaneous ventilation was restored when they were awakened by an auditory stimulus. Patients with brain damage also show apnoea after hyperventilation [18].

The study clearly demonstrates the effects of sedation on ventilatory control, predominantly neural control (awake) switching to predominantly chemical control (asleep or sedated). This information may have relevance in the occurrence of apnoea in a wide range of conditions from "cot death" to cardiorespiratory arrest during clinical procedures performed under sedation, especially if the patient is hypocapnic, from fear or pain. It may be a particular problem also in managing obstetric patients with Entonox. Post-hyperventilation apnoea following Entonox may be associated with hypoxaemia and impaired oxygenation of the fetus. It behoves clinicians to observe such patients closely and the use of pulse oximetry would be of benefit in such circumstances. It also supports the continued use of carbon dioxide cylinders on anaesthetic machines, which was the subject of a recent editorial in the Journal [19].

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ANTAGONISM OF INTENSE ATRACURIUM-INDUCED NEUROMUSCULAR BLOCK IN CHILDREN

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SUMMARY

Antagonism of intense neuromuscular block induced by atracurium 0.5 mg kg^{-1} was attempted in four groups of six children using one of two doses of neostigmine (0.05 mg kg^{-1} and 0.1 mg kg^{-1}) or of edrophonium (0.5 mg kg^{-1} and 1.0 mg kg^{-1}) when the first twitch of the post-tetanic count (PTC1) was 10% of control. For comparison with normal practice, a fifth group received neostigmine 0.05 mg kg^{-1} when the first twitch of the train-of-four was 10% of control. Total recovery time from PTC1 10% to a train-of-four ratio of 0.8 was not reduced by early administration of the anticholinesterases, compared with conventional administration of neostigmine at T1 10%. However, recovery from intense block was faster after neostigmine than edrophonium ($P < 0.01$). Doubling the doses of the anticholinesterases did not reduce the recovery time and had the effect of increasing variability. We conclude that there is no clinical advantage in attempting to antagonize intense neuromuscular block in children using normal or increased doses of neostigmine or edrophonium.

KEY WORDS

Anaesthesia paediatric. Antagonists · neuromuscular relaxants, edrophonium, neostigmine Monitoring. neuromuscular function.

It has been shown that pharmacological antagonism of neuromuscular block in adults and children may be accomplished reliably when the first twitch of train-of-four stimulation reaches 10% of the control twitch height [1, 2]. Despite claims that more profound levels of block may be antagonized easily [3], attempts to achieve this have usually met with failure [4–6]. This may reflect the use of long-acting neuromuscular blockers, ignorance of the level of block or the use of an inadequate dose of anticholinesterase. Moreover, there have been no studies in children, in whom both spontaneous and induced recovery from neuromuscular block is known to be faster than in adults [1, 7].

In the present study we have attempted to antagonize a quantified level of intense atracurium-induced neuromuscular block in children using either edrophonium or neostigmine.

PATIENTS AND METHODS

The study was approved by the District Ethics Committee. Thirty children aged 1–10 yr were studied during elective surgical procedures for which non-depolarizing neuromuscular blocking agents would be used normally as part of the anaesthetic technique. All were ASA class I and none was receiving drugs known to interfere with neuromuscular transmission. Patients were allocated randomly to one of five groups (A–E), to receive a predetermined dose of either neostigmine or edrophonium (table I).

Premedication with oral trimeprazine 3 mg kg^{-1} was given 2 h before surgery. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and maintained throughout with 66% nitrous oxide and 1% halothane in oxygen. Tracheal intubation was achieved without the aid of neuromuscular blocking drugs and ventilation of the lungs was controlled using the paediatric attachment of the Blease ventilator. Minute volume was adjusted to maintain the end-tidal carbon dioxide at 5.0–5.5 kPa. The ECG and systemic arterial pressure were monitored throughout the procedure and rectal temperature was kept at 36.5–37.5 °C.

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TABLE I. *Patient characteristics (mean (range)).* n = *6 in each group*

Group	Anticholinesterase	Age (yr)	Weight (kg)
A	Neostigmine 0.05 mg kg^{-1}	6.2 (3.9–9.6)	22.4 (15.5–29.5)
B	Neostigmine 0.1 mg kg^{-1}	4.2 (1.8–8.3)	17.1 (11.0–37.3)
C	Edrophonium 0.5 mg kg^{-1}	4.3 (3.0–6.5)	17.9 (11.8–28.9)
D	Edrophonium 1.0 mg kg^{-1}	3.8 (1.4–8.3)	15.2 (10.0–22.0)
E	Neostigmine 0.05 mg kg^{-1}	3.5 (1.4–7.2)	15.3 (10.8–25.5)

Neuromuscular transmission was monitored initially by train-of-four (TOF) stimulation [8] and force of adduction of the thumb measured using a Grass FTO3 force displacement transducer. After a 10-min period during which the response was allowed to stabilize, atracurium 0.5 mg kg^{-1} was administered. When the response to TOF stimulation had been abolished, neuromuscular transmission was monitored using the post-tetanic count (PTC) every 2 min [9]. When the first response of the PTC reached 10% of the control twitch height (PTC1 10%), patients in groups A–D received the predetermined dose of anticholinesterase, preceded by atropine 20 µg kg^{-1}. The method of monitoring in all groups then reverted to a TOF sequence every 12 s. Patients in group E were given neostigmine 50 µg kg^{-1} when the first twitch of the TOF reached 10% of the control twitch height (T1 10%). All patients were monitored until the TOF ratio reached 0.8 [10]. The following were determined from the recordings: interval PTC1 10% to T1 10%; interval T1 10% to TOF ratio 0.8; total recovery time, PTC1 10% to TOF ratio 0.8.

Differences between the groups were determined using the statistical package Minitab to fit a repeated measures analysis of variance (ANOVA) (Minitab Inc., 1989). A value of $P < 0.05$ was considered significant.

RESULTS

There were no significant differences between the five groups of children in age or weight (table I).

After administration of neostigmine or edrophonium at PTC1 10% (groups A–D) the time taken to reach T1 10% was shorter than when recovery was allowed to proceed spontaneously (group E) ($P < 0.001$) (table II). Recovery times from T1 10% to a TOF ratio of 0.8 were not significantly different with either dose of neostigmine or edrophonium. When data from these pairs of groups were combined, the T1 10% to TOF 0.8 interval was shorter in patients who received neostigmine ($P < 0.01$). However, the shortest T1 10% to TOF 0.8 interval was observed when neostigmine was administered at T1 10% ($P < 0.001$).

Data from groups who received neostigmine or edrophonium at PTC1 10% were combined also for analysis of total recovery time. The time was shorter after neostigmine than after edrophonium ($P < 0.01$) (table II). However, there were no significant differences in the total recovery times between groups when anticholinesterases were administered at either PTC1 10% or T1 10%. No patient in the present study required additional doses of atropine to treat bradycardia.

DISCUSSION

The results of the present study demonstrate that pharmacological antagonism of neuromuscular block in children is achieved best when the first twitch of the TOF has recovered spontaneously to 10% of the control twitch height. When antagonism was attempted at PTC1 10%, there was no clinically useful shortening of the recovery time with either neostigmine or edrophonium.

It has been demonstrated in adults and children that, when there is a degree of spontaneous recovery from neuromuscular block (T1 > 10%), antagonism of residual block can be achieved safely and is significantly faster after edrophonium than after neostigmine [1, 2, 11, 12]. Studies in adults have shown that when the degree of block is more profound (T1 < 10% or TOF < 0.1), complete antagonism is slower with edrophonium than with neostigmine [6, 13, 14]. However, in those studies, the degree of block at which antagonism was attempted was not accurately quantified. In order to overcome this problem, Engboek and colleagues measured recovery times after administration of neostigmine at various post-tetanic counts in adults [15]. They found

TABLE II. *Mean (range) recovery intervals after administration of anticholinesterases. Significant differences:* $^{**}P < 0.01$ *compared with edrophonium given at PTC1 10%;* $^{***}P < 0.001$ *compared with early antagonized groups*

Group	Anticholinesterase	Point of antagonism	PTC1 10% to T1 10% (min)	T1 10% to TOF 0.8 (min)	PTC1 10% to TOF 0.8 (min)
A	Neostigmine 0.05 mg kg^{-1}	PTC1 10%	2.4 (1.7–3.2)	11.8 (10.2–13.9)**	13.9 (12.2–15.5)**
B	Neostigmine 0.1 mg kg^{-1}	PTC1 10%	1.6 (1.4–2.1)	10.3 (5.7–14.2)**	11.9 (7.2–15.6)**
C	Edrophonium 0.5 mg kg^{-1}	PTC1 10%	1.2 (1.0–1.6)	18.8 (10.4–24.7)	20.1 (11.9–25.7)
D	Edrophonium 1.0 mg kg^{-1}	PTC1 10%	1.3 (0.9–1.8)	15.2 (6.3–26.9)	16.5 (7.4–28.1)
E	Neostigmine 0.05 mg kg^{-1}	T1 10%	9.7 (6.8–13.2)***	4.8 (3.2–7.5)***	14.3 (11.2–18.1)

that the more intense the block, the longer the time to a safe level of antagonism (TOF = 0.7). They concluded that early administration of anticholinesterase failed to antagonize neuromuscular block rapidly enough to be clinically useful.

In the present study, the administration of neostigmine or edrophonium at PTC1 10% resulted in an initial rapid recovery to T1 10%. Consistent with findings of earlier studies, initial recovery tended to be slightly quicker with edrophonium. This may be related to the smaller molecular weight of edrophonium allowing more rapid diffusion to the site of action [13]. In addition, edrophonium may function presynaptically to increase the output of transmitter from the nerve terminals [16]. Another possible explanation is provided by the Law of Mass Action, which states that the rate of reaction between a drug and receptor is proportional to the molar concentration of the drug [17]. The application of this principle to anticholinesterases may explain the more rapid onset after edrophonium, compared with neostigmine, as a much greater molar concentration of the former is used.

Although the initial antagonism of intense block (PTC1 10% to T1 10%) was rapid after both neostigmine and edrophonium, this was not maintained. Moreover, subsequent recovery (T1 10% to TOF 0.8) was significantly slower in patients who received edrophonium, possibly as a result of rapid depletion of acetylcholine stores by a presynaptic action of edrophonium [14]. Furthermore, the duration of action of edrophonium may be insufficient to sustain recovery when administered at profound levels of block [18]. This is supported by the fact that the recovery interval T1 10% to TOF 0.8 in children who received edrophonium (15.2–18.8 min) is similar to the times reported by Brandom and colleagues of 13–17 min for spontaneous recovery from atracurium-induced neuromuscular block in children [19].

The mean total recovery time of 13.9 min in children given neostigmine 50 μg kg^{-1} at PTC1 10% was much shorter than reported previously in adults (31 min) [15]. Increasing the dose of neostigmine had no significant effect on the total recovery time. However, patients who received the large doses of either neostigmine or edrophonium showed increased variability in total recovery time, consistent with previous findings in adults [15, 20].

In conclusion, the present study has demonstrated that there is no clinical advantage in attempting to antagonize intense neuromuscular block in children by administration of normal or increased doses of anticholinesterases. When compared with standard techniques of antagonism, the total recovery time was not reduced significantly and tended to become more unpredictable, particularly after edrophonium.

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HAEMODYNAMIC EFFECTS AND OUTCOME ANALYSIS OF HYPOTENSIVE EXTRADURAL ANAESTHESIA IN CONTROLLED HYPERTENSIVE PATIENTS UNDERGOING TOTAL HIP ARTHROPLASTY

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SUMMARY

We have examined the safety of induced hypotension produced by extradural anaesthesia in patients with medically controlled hypertension. The haemodynamic response to induced hypotension was assessed in 38 non-hypertensive and 31 controlled hypertensive patients. All received extradural anaesthesia to T4 or above which decreased mean arterial pressure to 52 mm Hg and 55 mm Hg in normotensive and hypertensive patients, respectively. Cardiac output (thermodilution) was maintained by low dose i.v. infusions of adrenaline (1–5 µg min^{-1}*). No differences in the haemodynamic response to induced hypotension were observed in hypertensive patients. Data were collected also from 987 consecutive patients (353 hypertensive and 634 non-hypertensive) undergoing total hip replacement. Patients with hypertension were significantly older (68 vs 60 yr;* $P < 0.001$*) and had greater ASA ratings (*$P < 0.001$*). The smallest recorded systolic pressures were reduced more in patients with hypertension (57% vs 52%, respectively;* $P < 0.001$*). The mean duration of maintained intraoperative hypotension (100 and 98 min) and estimated intraoperative blood loss (278 vs 281 ml) were similar in each group. After operation, two patients developed myocardial infarctions. None developed acute renal failure or stroke. There were three deaths; one of a patient who had hypertension. This suggests that induced hypotension with extradural anaesthesia is a safe technique for patients with medically controlled hypertension undergoing total hip arthroplasty.*

KEY WORDS

Anaesthetic techniques: extradural, hypotensive Complications: blood loss, myocardial infarction Surgery: orthopaedic.

The risk of HIV transmission has renewed interest in methods for minimizing perioperative homologous blood transfusion [1]. Although deliberate hypotensive anaesthesia has been shown to reduce intraoperative blood loss and transfusion requirements [2, 3], its use in the hypertensive patient remains controversial because of the potential risk of myocardial infarction, stroke or, possibly, renal failure [4].

Reduction in mean arterial pressure (MAP) may result in EEG changes secondary to a decrease in cerebral blood flow [5]. This is of particular concern in hypertensive patients who may have altered cerebral autoregulation [6, 7]. To circumvent this problem in elderly patients, a technique of inducing hypotension using extradural anaesthesia was developed, enabling mental status changes to be assessed during operation with the patient awake. The technique involves injection of sufficient doses of local anaesthetic into the extradural space to obtain upper thoracic levels of anaesthesia, resulting in a reduction of MAP. Circulatory stability is maintained thereafter throughout surgery by infusion of low dose adrenaline, which maintains cardiac output [8] and minimizes the risk of bradycardia [9].

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This study investigated this technique in patients with hypertension. This is important, as a significant percentage of patients undergoing total hip replacement are elderly and hypertensive [10].

PATIENTS AND METHODS

Following hospital Ethics Committee approval, we studied 1056 patients undergoing elective total hip arthroplasty under hypotensive extradural anaesthesia. In 69 of these patients haemodynamic measurements were obtained and in 987, a consecutive case group study was performed.

Patients were defined as hypertensive if they had been diagnosed by a physician as having hypertension necessitating treatment at some time before surgery. Patients with diastolic pressure of 110 mm Hg or greater on admission to the hospital had surgery delayed pending greater control of hypertension. All other patients were classified as non-hypertensive.

Haemodynamic measurements

The haemodynamic response to induced hypotension with extradural anaesthesia was measured in 31 patients who were admitted with a diagnosis of hypertension and in 38 non-hypertensive patients. Patients receiving β-blocking drugs (which are known to cause altered haemodynamic response to extradural anaesthesia [11]) or those with valvular heart disease were excluded. Of the 31 hypertensive patients, 29 were currently receiving antihypertensive treatment. Left ventricular hypertrophy (LVH) was defined by presence of left axis deviation with or without voltage criteria for LVH.

Indications for insertion of a pulmonary artery catheter included hypertension ($n = 31$), history of ischaemic heart disease ($n = 11$), congestive heart failure ($n = 1$), bilateral ($n = 11$) or revision ($n = 15$) total hip arthroplasy. The catheter was left *in situ* for 24 h.

Patients did not receive any premedication. On arrival in the operating room, they were sedated lightly with midazolam 1–3 mg and fentanyl 25–50 μg i.v. Patients received Ringer's Lactate 70 ml h^{-1} overnight, but not a fluid load before extradural anaesthesia, and they did not receive a volume greater than 200 ml of i.v. fluid between measurements. A 20-gauge radial artery catheter and the pulmonary artery thermodilution catheter were inserted under local anaesthesia using 1% lignocaine.

Patients were positioned in the lateral decubitus position and the transducers were positioned at the level of the midsternum. Heart rate, mean arterial, pulmonary artery and central venous pressures were recorded. Cardiac output was measured in triplicate using saline 10 ml at room temperature.

Extradural anaesthesia was performed at the L2–3 interspace by injecting 0.75% bupivacaine plain 15–25 ml via a 17-gauge Tuohy needle to achieve a sensory level to pinprick of T4 or above. An extradural catheter was inserted in all patients. Central venous infusions of adrenaline were started several minutes after the extradural injection in all patients as the arterial pressure began to decrease and the rate was adjusted (1–5 mg h^{-1}) to maintain a mean arterial pressure of 50–55 mm Hg. Ten to fifteen minutes after induction of a stable hypotensive state, haemodynamic measurements were repeated.

Consecutive case group

We studied prospectively 1016 consecutive patients undergoing elective total hip arthroplasty from January 1988 until April 1989. Twenty-seven patients who received general anaesthesia and 24 receiving spinal anaesthesia were excluded. The analysis included 987 patients receiving extradural anaesthesia; 353 patients had a pre-operative diagnosis of hypertension (86% were currently receiving antihypertensive medication) and 634 were not hypertensive.

Extradural anaesthesia was induced as described previously and all patients were monitored by direct arterial pressure recording. Mean arterial pressures were stabilized at 50–70 mm Hg by a combination of low dose adrenaline (1–5 μg min^{-1}) and i.v. fluids. In patients ($n = 267$) in whom MAP did not decline sufficiently, sodium nitroprusside was infused i.v. to induce hypotension. Patients were monitored continuously with pulse oximetry, V_5 ECG and radial artery pressure. Mental status was monitored intermittently throughout anaesthesia by conversing with the patient.

Hypotension during operation was assessed as follows: systolic pressures were recorded on arrival of the patient in the operating room and during operation (smallest systolic arterial pressure and that immediately before insertion of the femoral prosthesis). Intraoperative recordings of MAP were obtained from a monitor (Puritian Bennett 240- Wilmington, Mass. USA) which

TABLE I. *Clinical characteristics of 31 controlled hypertensive and 38 non-hypertensive patients*

	Hypertensive patients	Non-hypertensive patients	*P*
Sex (F/M)	21/10	19/19	
Age (yr) (mean (range))	71.8 (45–84)	69.2 (33–88)	
Height (cm) (mean (SD))	159.4 (10.9)	161 (14.4)	
Weight (kg) (mean (SD))	65.4 (11.8)	74.9 (21.8)	0.04
Arterial pressure on admission (mm Hg) (mean (SD))			
Sysolic	138.2 (13)	125.5 (8.82)	0.002
Diastolic	76.4 (6.3)	75 (6.63)	
Risk factors (No. (%))			
History of myocardial infarction	2 (6)	3 (8)	
History of other ischaemic heart disease	9 (29)	8 (21)	
History of congestive heart failure	5 (16)	1 (3)	0.05
Bundle branch block (ECG)	1 (3)	4 (11)	
ASA classification			
ASA I	0 (0)	5 (13.10)	0.01
ASA II	8 (25)	22 (57.80)	
ASA III	23 (75)	11 (28.90)	
ASA IV	0 (0)	0 (0)	

records data points every 20 s. From these recordings, sustained reductions in MAP from baseline were defined. These recordings were used to determine the duration and degree of induced intraoperative hypotension. Reduction in mean arterial pressures were categorized as 20–29%, 30–39%, 40–49%, or greater than 50%.

During closure of the wound, arterial pressure was increased by a combination of i.v. fluids and ephedrine. Blood loss was estimated by weighing swabs and measuring irrigation and drainage during operation.

Postoperative assessment

Patients with significant risk factors were maintained in an intensive care environment for 24–48 h, during which they received extradural analgesia and continued invasive haemodynamic monitoring. Patients with ischaemic heart disease had a 12-lead ECG recorded immediately after operation. Subsequently, ECG were recorded according to clinical needs. Surveillance of postoperative complications was performed through the hospital Quality Assurance programme, which screens all patients for adverse outcome. Death, acute renal failure, stroke and symptomatic Q wave myocardial infarcts ($Q > 0.03$ s) were defined as adverse outcomes.

Statistical analysis

Data are presented as means (SD). Contingency table analysis and one-way analysis of variance (ANOVA) were used to compare groups. The Mann–Whitney rank order test was performed for the ASA classification comparison. $P < 0.05$ was taken as statistically significant.

RESULTS

Haemodynamic study group

Patient characteristics are shown in table I.

Baseline haemodynamic data in hypertensive and non-hypertensive patients are shown in table II. Baseline MAP and systemic vascular resistance (SVR) were significantly greater in hypertensive than in non-hypertensive patients, whereas stroke volume (SV) was smaller. Cardiac output (CO), heart rate (HR), central venous pressure and mean pulmonary artery pressure were not significantly different. Following induction of hypotension during extradural anaesthesia, significant reductions in MAP, HR, pulmonary artery diastolic pressure, SVR and left ventricular stroke work index were observed. However, CO and SV remained unchanged in both groups (table II). When changes in haemodynamic variables from baseline to hypotensive state were compared between hypertensive and non-hypertensive patients, no significant difference was discernible (table II). To assess the effect of LVH on the haemodynamic response to induced hypotension during extradural anaesthesia, patients with and

TABLE II. *Comparison of the changes in haemodynamic variables between baseline and hypotensive state in controlled hypertensive and non-hypertensive patients (mean (SD)). Significant differences between hypertensive and non-hypertensive patients:* *$P < 0.05$; **$P < 0.01$

Haemodynamic variable	Hypertensive Baseline	 Hypotension	 Change	Non-hypertensive Baseline	 Hypotension	 Change
Cardiac index (litre min^{-1} m^2)	3.0 (0.6)	2.7 (0.6)	−0.3 (0.6)	3.3 (0.7)	3.0 (0.7)	−0.3 (0.9)
Mean arterial pressure (mm Hg)	110.7 (20 2)*	54.8 (7.5)	−55 9 (20 4)	100.0 (14 7)*	52 3 (6.6)	−47 7 (15 8)
Pulmonary artery diastole (mm Hg)	12.0 (5.0)	8.1 (3 7)	−3.9 (3.7)	10.6 (4.5)	8.2 (3 6)	−2.4 (3.0)
Heart rate (beat min^{-1})	78.6 (12.5)	70.0 (11.6)	−8.6 (12.9)	74.4 (13 8)	67.1 (12.5)	−7.3 (11.2)
Stroke volume (ml $beat^{-1}$)	68.0 (16 8)*	69.1 (20.8)**	1.1 (16.3)	79.7 (21.4)*	84.2 (21.3)**	4.5 (23.6)
Left stroke work index (g m m^{-2})	50.0 (13.2)	26.3 (9.3)	−23.7 (13.0)	54.8 (14.7)	28.0 (6.3)	−26.8 (15.1)
Systemic vascular resistance (dyn s cm^{-5})	1704.0 (59.8)*	937.0 (308.0)	−767.0 (419.0)	1398.6 (38.6)*	788.0 (365.0)	−610.6 (379 0)
Mean dose of adrenaline (μg min^{-1})		1.8 (1 3)			2 1 (1.2)	

TABLE III. *Comparison of haemodynamic response (mean (SD)) to hypotensive extradual anaesthesia in patients with (17) and without (52) ECG evidence of left ventricular hypertrophy (left axis deviation with or without voltage criteria)*

Haemodynamic variable	Left ventricular hypertrophy Baseline	 Hypotension	 Change	Control Baseline	 Hypotension	 Change
Cardiac index (litre min^{-1} m^{-2})	2.9 (0.6)	2 8 (0.8)	−0.1 (0 8)	3 2 (0.7)	3.0 (0.6)	−0.2 (0.9)
Mean arterial pressure (mm Hg)	107.7 (14.4)	53.2 (5.7)	−54.5 (13.4)	102.1 (18)	52.4 (6.6)	−49.7 (19.5)
Pulmonary artery diastole (mm Hg)	10 3 (4.8)	8.1 (3.3)	−2.2 (3.1)	10.2 (4.6)	7.0 (3.2)	−3 2 (3.5)
Heart rate (beat min^{-1})	76.3 (13 7)	69.3 (12)	−7.0 (8.6)	74.4 (13)	67.6 (13.7)	−6.8 (13.7)
Stroke volume (ml $beat^{-1}$)	69.2 (19 0)	72.6 (22.7)	3.4 (16.2)	77.3 (22)	80.1 (22.3)	2.8 (26.0)
Left stroke work index (g m m^{-2})	50.5 (12.3)	26.1 (7.4)	−24.4 (11.4)	54.8 (15)	28.0 (7.2)	−26.8 (16.7)
Systemic vascular resistance (dyn s cm^{-5})	1579.9 (450.4)	922 (418)	−657.8 (441.6)	1496 (562)	808.8 (308.8)	−687.2 (406 9)
Mean dose of adrenaline (μg min^{-1})		1.9 (1.4)			2.0 (1.2)	

without ECG criteria of LVH were compared. No significant differences were noted (table III).

Consecutive case group

Patients with hypertension were significantly older (68 *vs* 60 yr), had greater ASA ratings, a higher frequency of previous myocardial infarction, congestive heart failure, diabetes mellitus and bundle branch block (table IV).

The intraoperative changes in radial artery pressures are shown in table V. Patients with hypertension had significantly greater systolic pressure on arrival in the operating room (162.6 (27.2) mm Hg compared with 139.1 (21.5) mm Hg ($P < 0.0001$)). During operation the smallest recorded systolic pressures were 70.0 (11.8) and 67.6 (10.2) mm Hg. After femoral reaming, systolic pressures were 88.7 (13.5) and 83.6 (11.6) mm Hg, and peak reductions in systolic pressure were 57% compared with 52% ($P < 0.001$), in hypertensive and non-hypertensive patients, respectively. Similarly, systolic pressures before insertion of the femoral prosthesis were reduced by 45% and 40%, respectively, after reaming ($P < 0.001$). The mean duration of hypotension, expressed as change from the initial arterial

TABLE IV. *Clinical characteristics of 353 controlled hypertensive and 634 non-hypertensive patients undergoing extradural anaesthesia for total hip arthroplasty*

	Hypertensive patients	Non-hypertensive patients	*P*
Sex (F/M)	208/145	385/249	
Age (yr) (mean (range))	68.4 (30–93)	60.1 (14–92)	0.0001
No. (%) > 70 yr	179 (50)	150 (24)	
Height (cm) (mean (SD))	163.6 (11)	164.6 (12.2)	
Weight (kg) (mean (SD))	74 (16.8)	72 (16.5)	
Arterial pressure on admission (mm Hg) (mean (SD))			
Systolic	142 (19)	124 (16)	0.0001
Diastolic	82 (10)	75 (8)	0.0001
Risk factors (No. (%))			
History of myocardial infarction	33 (9)	30 (5)	0.004
History of other ischaemic heart disease	31 (9)	49 (8)	ns
History of congestive heart failure	13 (4)	3 (0.40)	0.0004
History of cerebral vascular accident	4 (1)	4 (0.60)	ns
History of diabetes	22 (6)	20 (4)	0.02
Atrial fibrillation	12 (3)	19 (3)	ns
Bundle branch block (ECG)	24 (7)	19 (3)	0.005
ASA classification			
ASA I	5 (1.40)	168 (26.40)	0.005
ASA II	230 (65.10)	367 (57.80)	
ASA III	116 (32.80)	97 (15.40)	
ASA IV	2 (0.50)	2 (0.30)	

TABLE V. *Comparison of radial artery pressures in 353 controlled hypertensive and 634 non-hypertensive patients before and during total hip arthroplasty under hypotensive extradural anaesthesia (mean (SD))*

	Hypertensive patients	Non-hypertensive patients	*P*
Initial (mm Hg)			
Systolic	162.6 (27.7)	139.1 (21.8)	0.0001
Diastolic	78.1 (12.5)	70.2 (11.6)	0.0001
Mean	105.6 (16.2)	92.8 (13.1)	0.0001
Smallest during op. (mm Hg)			
Systolic	70.0 (11.8)	67.6 (10.1)	0.008
Diastolic	41.5 (15.6)	39.0 (6.9)	0.007
Mean	51.0 (12.2)	48.6 (7.1)	0.0026
Before femoral cement (mm Hg)			
Systolic	88.7 (13.5)	83.6 (11.6)	0.0001
Mean	62.0 (9.5)	58.6 (8.9)	
Duration of hypotension (min)	100.0 (56.4)	98.2 (51.8)	ns
Estimated blood loss during op. (ml)	278.0 (169.0)	281.0 (182.0)	ns

cannula MAP was 100 (56.4) min in hypertensive patients and 98 (51.8) min in those without hypertension (table VI).

Complications

There were three deaths (0.3%) in the postoperative period. One patient, who had hypertension, died 46 h after operation, following an acute anterior wall myocardial infarct. Two other patients who did not have hypertension died, one from aspiration 36 h after operation, and the other on the 5th day after operation, as a result of acute pulmonary embolism. One other patient developed a Q wave inferior wall myocardial infarct 24 h after operation. Both patients who developed Q wave myocardial infarcts had histories of ischaemic heart disease, but only one was hypertensive.

Although one patient with preoperative renal dysfunction had an increase in serum creatinine

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TABLE VI. *Duration (mean (SD)) and degree of sustained hypotension (expressed as percentage reduction in MAP from arrival in the operating room) maintained in 987 patients undergoing total hip arthroplasty*

	Hypertensive patients		Non-hypertensive patients	
Degree of hypotension	No. (%) of patients	Duration (min)	No. (%) of patients	Duration (min)
< 20%	46 (13)	109.1 (62.8)	61 (10)	111.0 (62.2)
20–29%	8 (3)	95.6 (63.6)	45 (7)	94.6 (61.2)
30–39%	55 (15)	103.0 (58.8)	160 (25)	95.6 (47.7)
40–49%	107 (30)	104.2 (51.8)	195 (31)	101.6 (50.6)
50% or greater	137 (39)	90.2 (45.2)	173 (27)	86.0 (37.7)
Mean		100.0 (56.4)		98.2 (51.8)

(from 2 to 2.8 mg dl^{-1}) on the 3rd day after operation, no patient developed stroke or acute renal failure after operation.

DISCUSSION

The reductions in mean arterial pressure of 40–50% after extradural anaesthesia were tolerated well in our patients with medically controlled hypertension. Furthermore, intraoperative hypotension lasting an average of 98 min during total hip replacement did not result in any measurable increase in adverse outcome. These observations suggest that medically controlled hypertension is not a contraindication to induced hypotension using extradural anaesthesia.

Many anaesthetists question whether or not hypotensive anaesthesia should be used in patients with hypertension [2, 4, 12] because of the risk of cerebral hypoperfusion [13], myocardial infarct [14] or renal failure [15]. Untreated severe hypertension leads to widespread structural and physiological changes in the circulatory system. These include hyperplasia of the media of arterioles [16], left ventricular hypertrophy [17], alterations in autoregulation of regional blood flow [18] and reduction in the circulating blood volume [19]. In this setting, hypotensive anaesthesia may lead to reduction in cardiac output and tissue hypoperfusion [20]. However, with adequate control of hypertension ventricular hypertrophy resolves [21], autoregulation of cerebral blood flow may become normal [7] and blood volume expands. This may explain why the haemodynamic response to induced hypotension with extradural anaesthesia was not significantly different between treated controlled hypertensive patients and non-hypertensive patients.

The consequences of a reduction in cerebral blood flow are difficult to assess during general anaesthesia. Strandgaard noted in awake humans that clinically significant reductions in cerebral blood flow resulted in nausea, yawning, confusion, hyperventilation and, if not corrected, unconsciousness [7]. He attributed these symptoms to reductions in cerebral blood flow secondary to hypotension. However, the techniques used to decrease arterial pressure in his patients also reduced cardiac output. In our experience, these signs have not been observed in hypertensive patients at mean arterial pressures of 50 mm Hg with adequate cardiac output. However, we have observed these symptoms when the cardiac index decreased to less than 1.8 litre min^{-1} m^{-2}. This implies that the safety of induced hypotension with extradural anaesthesia is dependent upon adequate cardiac output and the ability to monitor cerebral function.

Patients with ventricular hypertrophy may be at risk of developing subendocardial ischaemia [19, 21] or reduction in cardiac output [22] during induced hypotension. We attempted, therefore, to classify patients into two groups: those with and those without ventricular hypertrophy. As we were unable to perform echocardiographic determination of ventricular mass [17], ECG criteria alone were used. Surprisingly, patients with ECG criteria of LVH did not respond differently to induction of hypotension during extradural anaesthesia. This may imply that, as coronary perfusion pressure decreases, reductions in wall tension occur which are sufficient to preserve supply/demand relationships [23]. We also observed preservation of stroke volume in spite of a reduction in preload. This may represent improved systolic emptying from reduced afterload [24].

Two (1.3%) of the 153 patients with a preoperative diagnosis of ischaemic heart disease developed myocardial infarctions after operation. As only one of these patients had hypertension, it does not appear that hypertension *per se* predisposed patients to postoperative Q wave myocardial infarction. Rates of clinically apparent myocardial infarction following major surgery vary from 0.1 to 0.7% [25]. In spite of our high risk population, only 0.2% had postoperative Q wave myocardial infarction, which suggests either that the risks of perioperative myocardial infarction after total hip replacement are low, or that induced hypotension during extradural anaesthesia does not increase the incidence of myocardial infarction.

Several other factors may have contributed to the low risk of myocardial infarction in this group. All patients received aspirin 325 mg twice daily after operation. Most patients with histories of arteriosclerotic heart disease or congestive heart failure had pulmonary artery monitoring for 24 h after operation and were kept pain free for 12–24 h after operation with extradural infusions of fentanyl and bupivacaine. Hospital mortality rates after total hip replacement range from 0.3% to 2.8% [26, 27]. The major causes of death are pulmonary embolism [28] (up to 3.5%), myocardial infarction and respiratory failure/pulmonary oedema [29]. It would appear, therefore, that induced hypotension during extradural anaesthesia does not increase, but may help to decrease, perioperative mortality. It is difficult, however, to draw conclusions when comparing historical death rates between different hospitals.

Renal failure is an uncommon sequela of hypotensive anaesthesia [30], and only one patient in this series developed an increase in serum creatinine concentration after operation. He had pre-existing mild renal dysfunction, and the increase was probably unrelated to the anaesthesia. Hypertensive patients with renovascular disease may develop oliguria during hypotensive anaesthesia [4].

Stroke is a major complication of untreated hypertension [31]. Because of concern regarding autoregulation of cerebral blood flow, many anaesthetists avoid hypotensive anaesthesia in hypertensive patients [7]. However, many strokes are either embolic or haemorrhagic in aetiology and not related to hypotension *per se* [32]. Ability to preserve cardiac output and monitor cerebral function by conversing with awake patients should make hypotensive extradural anaesthesia more acceptable.

Extradural anaesthesia may offer several advantages for total hip surgery, including reduction in intraoperative blood loss [2, 3], perioperative homologous transfusion requirements [3, 33] and thromboembolism [34]. Induced hypotension may also improve fixation of cemented components [35] and reduce the likelihood of hypotension following insertion of a cemented prosthesis [36]. Other methods of reducing requirements for homologous transfusion include preoperative autologous blood donation, intraoperative salvage or haemodilution, and administration of erythropoietin before operation [37].

Previous studies have suggested that episodes of hypotension are associated with an increased incidence of perioperative myocardial infarction [14, 38]. However, the monitoring techniques used were usually non-invasive and the hypotension often secondary to underlying disease or shock. Recent studies in patients undergoing coronary artery bypass graft surgery have shown that tachycardia [25, 39] rather than hypotension is most likely to precipitate ischaemia, and that postoperative myocardial infarction usually develops in patients with pre-existing ischaemia and is not related merely to variation in haemodynamic state [40]. Our experience suggests that arterial pressure reduction of up to 50% during extradural anaesthesia did not result in adverse outcomes when associated with satisfactory cardiac output, blood volumes and heart rate.

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COMPARISON OF INVASIVE AND NON-INVASIVE MEASUREMENT OF CONTINUOUS ARTERIAL PRESSURE USING THE FINAPRES

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SUMMARY

A comparison was made of arterial pressures measured invasively from a radial arterial cannula and non-invasively from the middle finger using the 2300 Finapres (Ohmeda) during induction and maintenance of anaesthesia. Digital outputs of both pressures were captured directly onto computer hard disk; data recorded during flushing of the arterial line were excluded from analysis. We studied 53 patients undergoing cardiac, major vascular and neurosurgical procedures; 17705 comparisons of systolic, diastolic and mean pressure were analysed. Overall correlations between Finapres and invasive pressures were poor (r = 0.82, 0.68 and 0.78 for systolic, diastolic and mean pressures, respectively). The Finapres exhibited a high level of accuracy and precision in some recordings. However, patient data sets showed marked variability in average pressure differences (invasive minus Finapres) when examined individually or grouped by operation type. Unexplained variations in pressure difference with time and absolute pressure were observed also. Whilst providing useful beat-to-beat information on arterial pressure trends, the Finapres cannot be recommended as a universal substitute for invasive arterial pressure monitoring.

KEY WORDS

Measurement techniques: arterial pressure Monitoring: arterial pressure, Finapres

Invasive beat-to-beat arterial pressure monitoring is practised widely in anaesthesia and intensive care. Although it is considered generally to be a low-risk, high-benefit monitoring technique [1], serious complications may develop after radial artery cannulation [2]. In 1973, Penaz described a method whereby a continuous non-invasive arterial pressure waveform could be obtained from a finger cuff [3]. This idea was developed by the Dutch Biomedical Instrumentation Group of TNO [4] and the first prototype finger arterial pressure monitor (Finapres; Ohmeda) emerged in 1982 [5].

The finger cuff incorporates a photo-plethysmograph with an infra-red light emitter and detector. The wavelength detected is characteristic of that absorbed by haemoglobin, allowing arterial pulsations to be sensed. The principle of operation involves "volume-clamping" of the finger whereby cuff pressure is adjusted rapidly under feedback control to keep the infra-red signal at constant amplitude and hence the finger at constant blood volume over the arterial pressure cycle. Initially, the cuff pressure is inflated in steps until the maximum amplitude pulsation is recorded (open-loop mode), which is taken to be equivalent to mean arterial pressure. Thereafter a servo control loop with a delay time of 10 ms rapidly adjusts finger cuff pressure to keep the intensity of the infra-red signal constant (closed-loop mode). In order to do this, cuff pressure must balance digital intra-arterial pressure over the whole pressure cycle, hence keeping the transmural pressure across the arterial wall at zero. Fluctuations in cuff pressure are transduced

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and displayed as a continuous waveform. The servo control system is adjusted automatically every 1 min during operation to compensate for changes in finger interstitial fluid and blood volume and changes in arterial smooth muscle tone. The digital display of pressure may be updated "beat-by-beat" or averaged over 6 s.

A clinical evaluation of the 2300 Finapres (FINger Arterial PRESsure; Ohmeda) Blood Pressure Monitor is described using a computer-based system during induction and maintenance of anaesthesia. The aim of this study was to establish if the data obtained by the Finapres are sufficiently reliable to form a basis on which clinical management decisions can be made.

PATIENTS AND METHODS

Patients undergoing induction of anaesthesia for cardiac, major vascular and neurosurgery were studied. These subjects were chosen primarily because they routinely undergo arterial cannulation before the induction of anaesthesia. Furthermore, an opportunity was afforded to compare the performance of the Finapres in healthy (neurosurgical) and diseased (cardiac and vascular) cardiovascular systems at a time of haemodynamic instability. Further recordings during maintenance of anaesthesia were undertaken in neurosurgical patients over a period of up to 3 h. No patient received vasoactive drugs during the study. Anaesthetic techniques were not standardized.

Measurement of pressures

Direct intra-arterial pressure was measured from the radial artery of the non-dominant hand after insertion of a 20-gauge Teflon catheter (Abbocath or Viggo) connected via a 1.2-m long, 1.5-mm diameter extension to a disposable transducer (CR Medicals, Bordon). Before each case, the transducer was fixed at the level of the Finapres electropneumatic transducer then zeroed and calibrated to 200 mm Hg using a mercury column. The arterial waveform was displayed on a Hewlett–Packard 78353B monitor. Calibration was checked also after each set of recordings. The frequency response of the system was flat to 12 Hz.

Non-invasive pressure was measured with a pre-calibrated 2300 Finapres Blood Pressure Monitor (Ohmeda). The Finapres cuff was applied to the middle phalanx of the middle finger on the same side or side opposite to the arterial line after measurement of finger circumference. A medium sized cuff was applied unless an unsatisfactory fit was obtained, in which case a more appropriately sized cuff was used. The box containing the Finapres electropneumatic transducer was strapped to the back of the hand, which rested by the patient's side during recordings. Both transducers were secured throughout the study period. The Finapres digitized output was set to "beat-to-beat". Recordings were commenced after a stable Finapres signal had been obtained and discontinued at the time when the patient was transferred to the operating theatre. Maintenance recordings were commenced after positioning the patient for surgery and discontinued after 3 h or at completion of surgery.

Data collection

Simultaneous digitized outputs from the Hewlett–Packard 78353B monitor and Finapres RS232C interface were stored as ASCII files on the hard disk of a Hermes 100 IBM-compatible PC (fig. 1) using a program developed in this department by one of the authors (C.P.). This program captured simultaneously systolic, mean and diastolic pressures from both sources, together with other variables such as heart rate. A sampling interval of 3 s was selected for induction recordings and 30 s for maintenance recordings.

Data handling

Data files for each patient were re-formatted for statistical analysis using statistical software packages (Statgraphics: Statistical Graphics Corporation; Minitab: Minitab Inc.; Complete Statistical System: Statsoft). Artefactual values recorded during flushing or sampling from the arterial line were edited out of each recording. Readings during the Finapres "lock-out" routine which occurs once every 70 beats were not edited—the Finapres displays the values for the preceding beat during this procedure.

Various aspects of the performance of the Finapres were investigated by analysis of the resulting data:

(1) To assess if the Finapres gave a good overall estimate of radial arterial pressure, linear regression was performed on all systolic, diastolic and mean pressure comparisons and 95% confidence intervals were calculated for the line. In view of the considerable inter-individual variability, further analysis was undertaken in order to

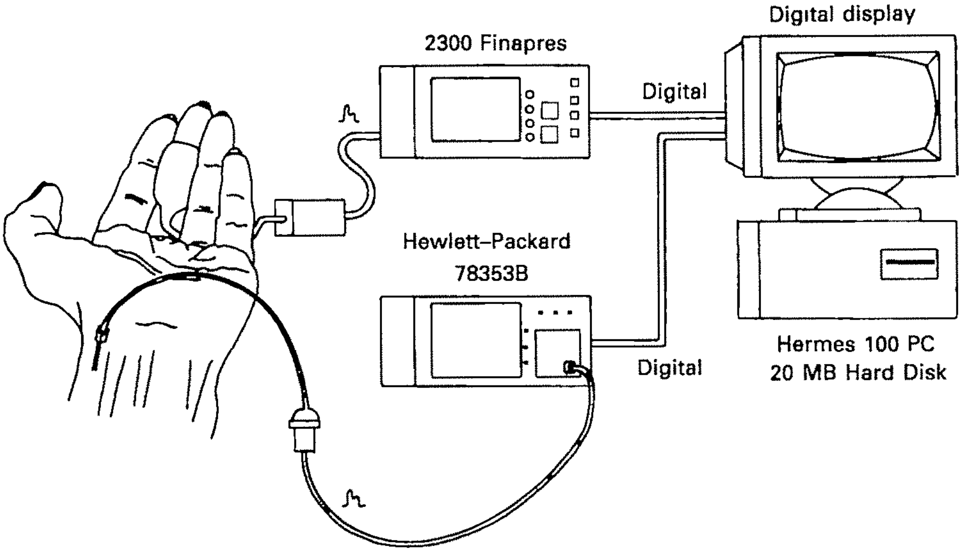

FIG. 1. Experimental arrangement for display and storage of simultaneous Finapres and invasive pressure readings.

establish how accurate, precise and reproducible Finapres readings were in individual patients.

(2) Systolic, diastolic and mean pressure differences (invasive minus Finapres readings) were calculated for each individual patient record. The average of this difference for each record was plotted against its SD in order to display the scatter of the data. Further analyses examined the influence of cuff size, finger circumference, cuff position and type of surgery on between-patient variability.

(3) The pressure differences were plotted against their averages [6] and the "limits of agreement" (mean (2 SD)) were calculated to assess variability with changing pressure.

(4) Time series plots of paired invasive and non-invasive pressures (systolic, diastolic and mean) were displayed from each recording. Time series analysis of the differences between each pair of pressures (invasive minus Finapres) was undertaken to investigate temporal variability.

(5) Simultaneous first order differential pressures were calculated at 30-s intervals for each pressure and displayed as scatterplots of invasive *vs* Finapres differential pressure (systolic, diastolic and mean) for each record. The frequency with which changes in Finapres readings occurred in phase with changes in invasive readings (i.e. an increase in Finapres pressure accompanied by a simultaneous increase in invasive pressure and *vice versa*) was calculated for each record. This analysis established how often Finapres and invasive pressures moved in the same direction simultaneously.

Data were analysed using Spearman's rank correlation coefficient and Fisher's exact, chi-square, Mann–Whitney and unpaired Student's *t* test where appropriate.

RESULTS

We studied 53 patients (age range 18–75 yr) (table I). The Finapres displayed a waveform which resembled an arterial pressure trace in all cases. Finapres and invasive pressures were measured from the same arm in 24 patients (45.3%). Finger circumference was in the range 38–73 mm, but did not differ significantly between patients grouped by operation type ($P > 0.05$). A total of 17705 comparative pressure readings was available for statistical analysis.

Linear regressions

Linear regression analysis between the Finapres and invasive pressure measurements of all paired systolic, diastolic and mean pressures demonstrated correlation coefficients of $r = 0.82$, 0.68 and 0.78, respectively (fig. 2). Clearly, the Finapres does not always reflect invasive arterial pressure faithfully in all patients.

TABLE I. *Details of patients studied. Numbers in parentheses denote the number of patients within each group in whom Finapres data and invasive pressure were measured from the same arm. S = Small; M = medium; L = large*

Operation	No. patients (M/F)	Mean age (yr)	Induction	Maintenance	Finapres cuff size S	M	L
Neurosurgical	11/9	49 6	15 (7)	19 (6)	1	18	1
Cardiac (CABG)	13/3	60.3	16 (5)	—	3	10	3
Cardiac (valve)	8/4	53 7	12 (8)	—	2	9	1
Major vascular	4/1	62.8	5 (4)	—	—	5	—

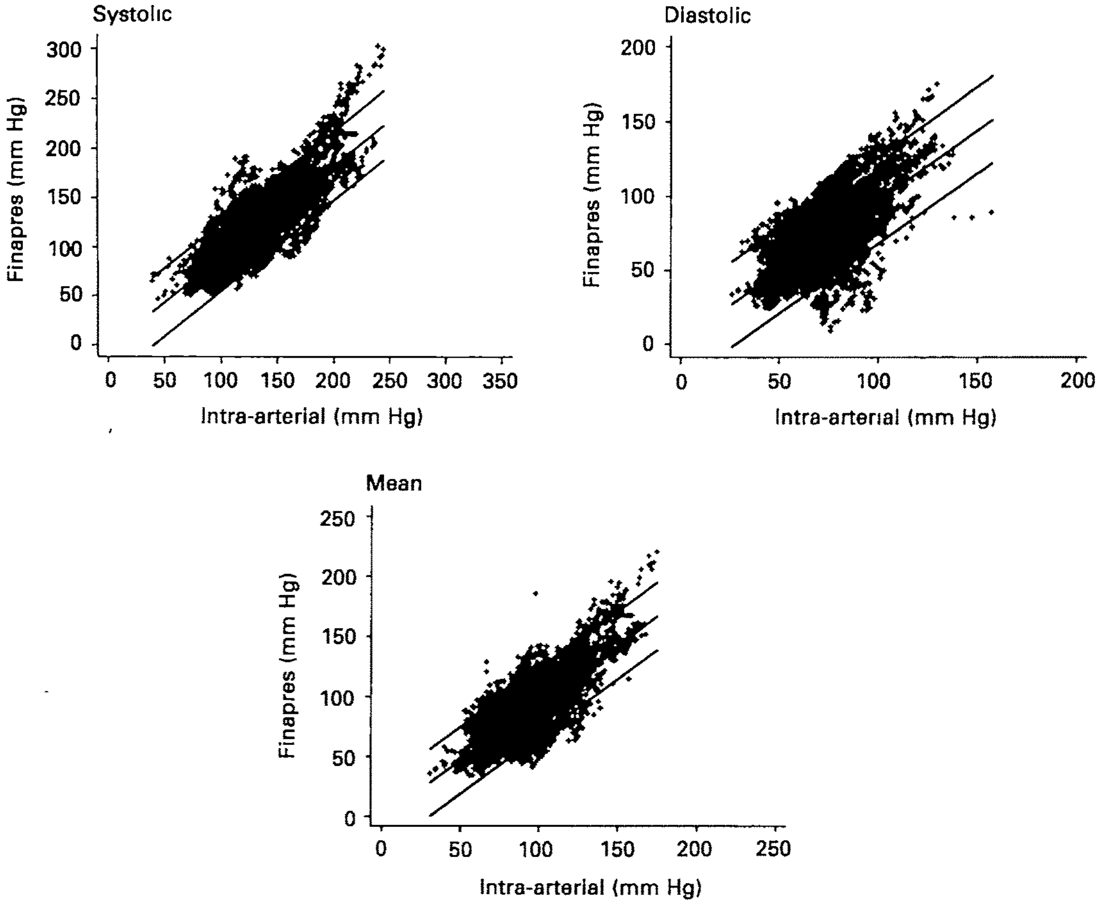

FIG. 2. Linear regression lines (with 95% confidence limits (CL) about the mean) for all comparisons ($n = 17705$) of Finapres and invasive monitoring of systolic, diastolic and mean arterial pressures in the study population. Systolic: $r = 0.82$; $y = 0\ 92x-2.37$; 95% CL = ±34.1 mm Hg. Diastolic: $r = 0.68$; $y = 0.95x+2.75$; 95% CL = ±28 3 mm Hg. Mean: $r = 0.78$; $y = 0.96x-1\ 43$; 95% CL = ±27.5 mm Hg.

Between-patient variability

In order to examine the variability between individual patients, the average pressure difference (invasive minus Finapres) for each patient was plotted against its SD. Separate scatterplots were obtained for systolic, diastolic and mean pressures (figs 3–5). They show considerable

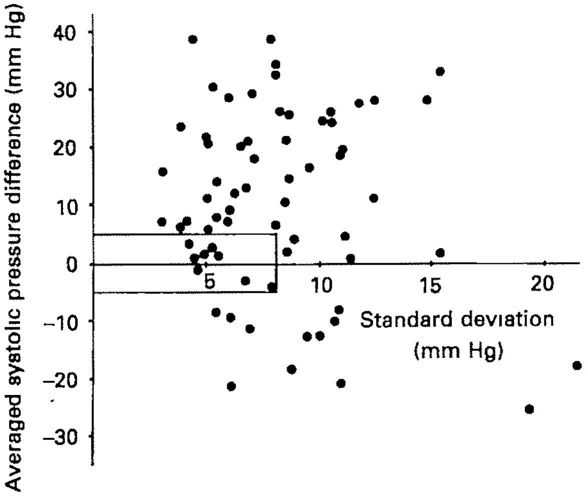

FIG. 3. Scatterplot of the average difference in systolic pressure (invasive minus Finapres) against SD for individual patient records ($n = 67$). Data points within the "box" conform to ANSI standards [7].

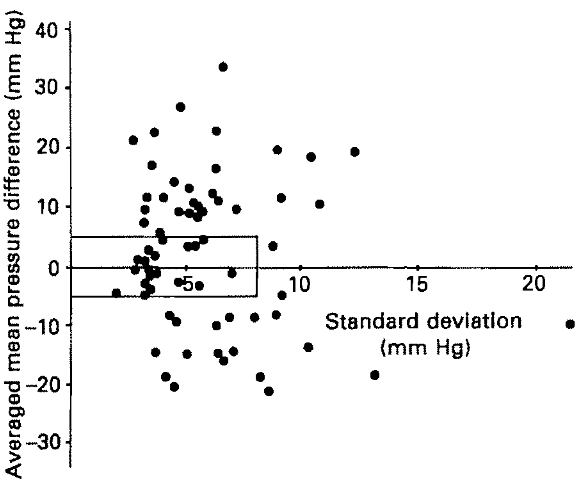

FIG. 5. Scatterplot of the average difference in mean pressure (invasive minus Finapres) against SD for individual patient records ($n = 67$). Data-points within the "box" conform to ANSI standards [7].

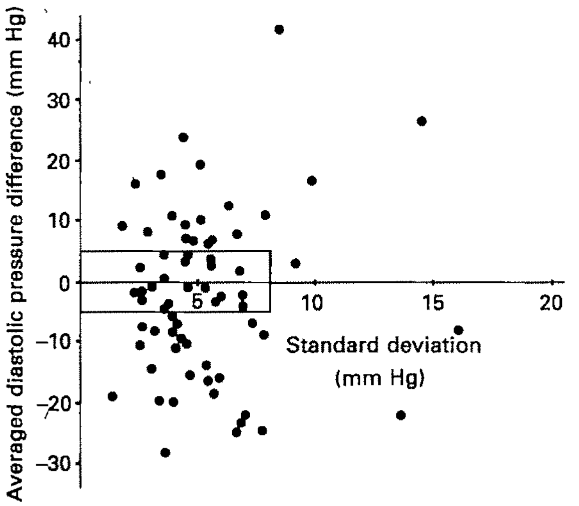

FIG. 4. Scatterplot of the average difference in diastolic pressure (invasive minus Finapres) against SD for individual patient records ($n = 67$). Data points within the "box" conform to ANSI standards [7].

scatter in the accuracy (average difference) and precision (SD) of the Finapres. The American National Standards Institute (ANSI) has recommended limits for the accuracy of automated non-invasive arterial pressure devices when compared with invasive pressure [7] and these were superimposed onto the scatterplots. Only 11.9, 29.9 and 28.4% of patient records fulfilled the ANSI recommendations for systolic, diastolic and mean pressure differences, respectively. Diastolic pressure differences showed less variability than systolic or mean differences. The predominance of positive systolic average pressure differences demonstrates that the Finapres under-reads systolic pressure in many cases.

Finapres cuff size, cuff position and type of surgery (with the exception of major vascular procedures) had no effect on the proportion of patient recordings which conformed to ANSI standards (Fisher's exact and chi-square tests). However, these factors undoubtedly accounted for some of the observed variability. Under-reading of systolic pressure was significantly greater when large finger cuffs were used (unpaired Student's t test). There was no relationship between finger circumference and the magnitude of the average pressure difference (correlation coefficients $r =$ 0.25, 0.1 and 0.14 between finger circumference and systolic, diastolic and mean pressure differences, respectively). Positioning of the Finapres cuff in relation to the radial arterial cannula (contralateral or ipsilateral) was responsible for variability between patients undergoing the same type of operative procedure. When contralateral and ipsilateral cuff placements were compared, averaged pressure differences (Finapres minus invasive) differed significantly within each group of operative procedures except systolic and diastolic pressures during induction for neurosurgical procedures (unpaired Student's *t* test; Mann–Whitney test). There was no consistent pattern to the observed differences.

There were significant between-group differences for all comparisons made of pressure differences grouped by operation type (fig. 6). Recordings from neurosurgical cases during induction of anaesthesia showed the greatest scatter of readings. Scatter was least marked for recordings from major vascular cases, probably because of the small number of patients in this group.

Variability with pressure

To investigate the accuracy and precision of the Finapres over a range of pressures, the pressure differences were plotted against simultaneous average pressure for individual patient records using the method recommended by Bland and Altmann [6]. Considerable bias was observed in many of the resulting plots. In more than 50% of the individual plots for systolic, diastolic and mean pressures there was no relationship between pressure difference and average pressure. The remaining plots displayed a variety of relationships. The pressure difference decreased with increasing average pressure in 25% of cardiac (CABG) patient records (fig. 7) and showed increased scatter with increasing average pressure in 47% of records from patients undergoing major vascular surgery (fig. 8).

Variability with time

Time series plots of systolic, diastolic or mean absolute comparative pressures and pressure differences during maintenance recordings demonstrated marked variability in pressure difference with time. Baseline drift characterized by a decreasing pressure difference was identified in 53% of recordings when the trend was not obscured by fluctuations attributable to variations in absolute pressure. Baseline drift averaged -7.8 mm Hg h^{-1} (range -2.5 to 15 mm Hg h^{-1}) affecting systolic, diastolic and mean pressure differences to a similar extent (fig. 9) in all but one recording. No baseline drift was identified in the calibration of the invasive pressure measurement system, suggesting that Finapres readings increased in magnitude relative to invasive measurements over time.

Reliability of trend information

To establish if trend information from the Finapres was reliable, 6467 comparative Finapres

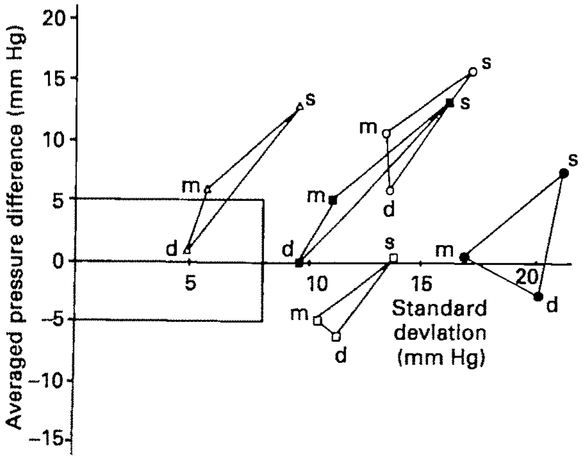

FIG. 6. Scatterplot of the average differences in systolic (s), diastolic (d) and mean (m) arterial pressures (invasive minus Finapres) against SD grouped by operation type: ○ = cardiac (coronary grafts); ■ = cardiac (valves); △ = major vascular; ● = neurosurgical (induction); □ = neurosurgical (maintenance). Data points within the "box" conform to ANSI standards [7].

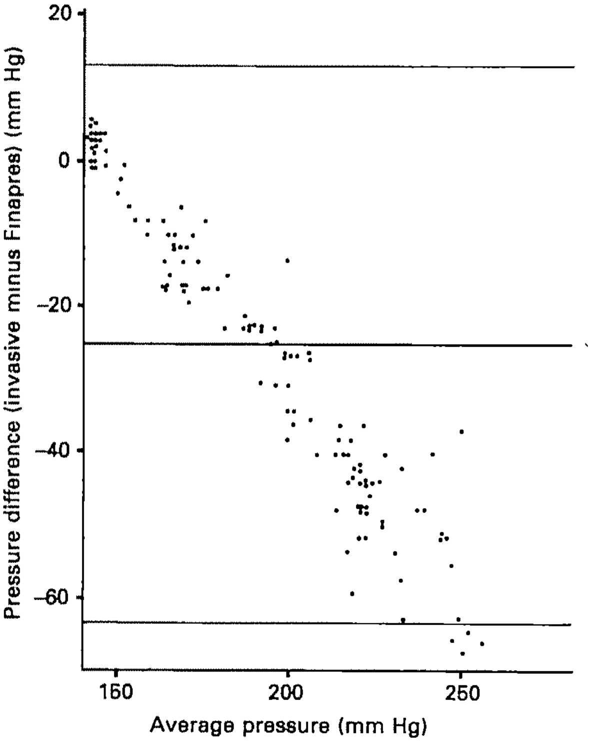

FIG. 7. Scatterplot of systolic pressure differences against simultaneous average pressure from a single patient record (after Bland and Altmann [6]). The pressure difference decreases with increasing average pressure in a linear fashion.

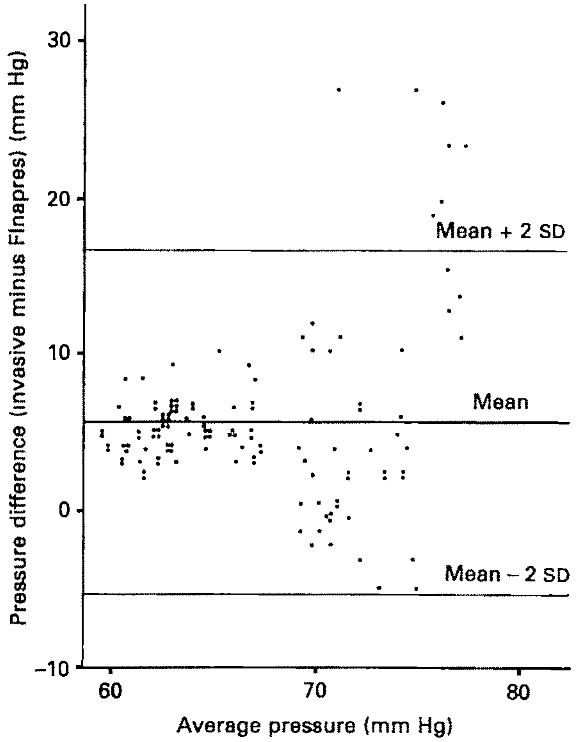

FIG. 8. Scatterplot of mean pressure differences against simultaneous average pressure from a single patient record (after Bland and Altmann [6]). The pressure difference shows increasing variability as the average pressure increases.

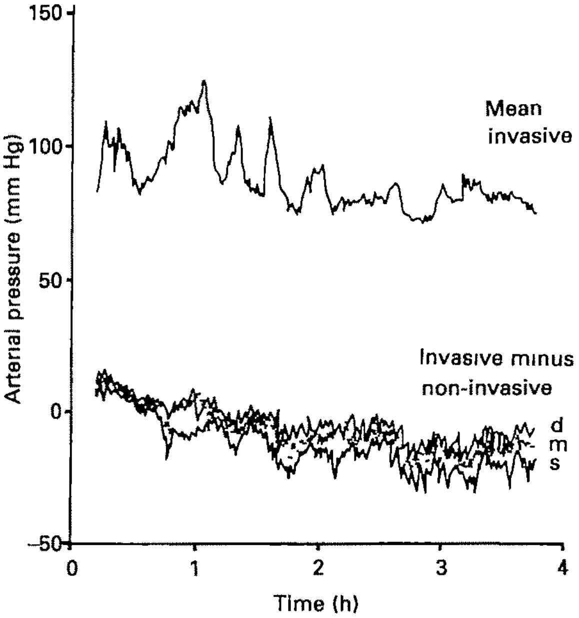

FIG. 9. Time series plot from a single patient record showing baseline drift of systolic, diastolic and mean pressure differences during maintenance of anaesthesia for neurosurgery. The mean invasive pressure is plotted also, for comparison.

and invasive first order pressure differentials were analysed from all patient records. Finapres and invasive comparisons of systolic, diastolic and mean differential pressure were in phase for 81.1, 84.4 and 85.6% of readings, respectively. Conversely, this analysis implies that Finapres pressure was increasing whilst invasive pressure was decreasing (or *vice versa*) for 18.9, 15.6 and 14.4% of readings of systolic, diastolic and mean pressure, respectively. Finapres systolic pressure was less likely to follow invasive pressure than mean or diastolic pressures in all patient groups (table II), but differences were not significant (chi-square).

TABLE II. *Number (%) of first order differentials of Finapres pressures moving in the direction opposite to the simultaneous differentials of invasive pressure readings (no significant differences; chi-square test)*

		Number (%) moving out of phase		
Operation	Total	Systolic	Diastolic	Mean
Cardiac				
Valves	785	126 (16.1)	132 (16.8)	98 (12.5)
CABG	1106	206 (18.6)	153 (13.8)	158 (14.3)
All	1891	332 (17.6)	285 (15.1)	256 (14.3)
Major vascular	378	56 (14.8)	32 (8.5)	40 (10.6)
Neurosurgical				
Induction	337	58 (17.2)	47 (14.0)	41 (12.2)
Maintenance	3861	74 (20.1)	645 (16.7)	592 (15.3)
All	4198	832 (19.8)	692 (16.5)	633 (15.1)
Totals	6467	1220 (18.9)	1009 (15.6)	929 (14.4)

Examination of time series plots did not demonstrate any consistent phase lag between Finapres and invasive pressure changes to account for these discrepancies.

DISCUSSION

Clearly, digital arterial pressure differs from that measured in the radial or brachial arteries and this difference has not been characterized in man. In order to be accepted as a basis for making clinical decisions, the Finapres must be shown to display values which are identical or approximate closely to readings obtained from either an indwelling catheter or a brachial cuff. It is therefore logical to compare Finapres and intra-arterial readings.

Since Wesseling developed the first Finapres device in 1982, studies comparing its accuracy with directly measured arterial pressure have been published by several groups [8–11]. Whilst being informative, these studies have shortcomings and are of limited relevance to the clinical application of the Finapres. All used analog signals for data collection and output was sampled either at predetermined points [8–10] or over a limited period of time [11]. Smith, Wesseling and de Wit [8] analysed mean pressure comparisons only during stable anaesthesia. In the present study, digitized outputs from Finapres and invasive monitors were captured directly onto computer hard disk (fig. 1). Little attempt was made to edit our data, other than rejecting artefactual values recorded by the Hewlett–Packard monitor during flushing of the arterial cannula. All the remaining pressure recordings were included for analysis. The resulting comparisons constitute a true reflection of the performance of the Finapres in anaesthetic practice. Furthermore, no previous studies have assessed the Finapres during induction of anaesthesia, when large changes in arterial pressure occur rapidly.

Statistical analysis in previous studies [8–10] has centred on linear regression and correlation, which have been shown to be inappropriate when comparing two measurement techniques which are subject to variability [6].

Several fundamental requirements of a non-invasive continuous monitoring system merit further discussion in relation to the Finapres.

Quality of signal, accuracy and precision

Assessment was made of the ease with which a reliable signal could be obtained in different patients, including groups with low cardiac outputs and abnormal peripheral vasculature. In all patients studied, a recognizable waveform was obtainable, within 1 min of activating the Finapres when an appropriately sized finger cuff had been applied. Under-reading of systolic pressure by the Finapres was apparent in cardiac patients and those with arteriopathies, compared with neurosurgical patients ($P < 0.05$).

The morphology of the systemic arterial waveform depends on the site of measurement in the arterial tree. More distal readings should be characterized by a smaller mean pressure, a change in shape caused by pulse wave reflections, increased damping and a wider pulse pressure [8]. Paradoxically, narrower pulse pressures were obtained using the Finapres compared with invasive measurements in cardiac patients and arteriopaths. Low cardiac output associated with compensatory increases in peripheral vascular resistance could explain these findings, although diastolic pressures did not differ as greatly as systolic pressures. Vasoconstriction induced by the infusion of phenylephrine has been shown to reduce mean arterial pressure measured by the Finapres without affecting invasive pressure [9].

Significant within-group differences were observed between readings obtained from contralateral and ipsilateral cuff placement in cardiac and major vascular patients ($P < 0.05$). Possible explanations include between-arm differences in systemic arterial pressure and reductions in blood flow distal to a cannulated radial artery. Finapres readings usually returned to pre-cannulation values within 4 min of radial artery cannulation [12], so the effects of insertion of an arterial cannula do not explain these differences. Furthermore, averaged Finapres readings of systolic, diastolic and mean pressure were greater than invasive pressures when measured in the cannulated arm of cardiac patients.

There are no internationally recognized standards for assessing the performance of automated non-invasive arterial pressure devices. The American National Standards Institute [7] have suggested that a mean difference of no greater than ±5 mm Hg with an SD of 8 mm Hg should exist between readings obtained from the device under test and the standard device. The standard makes allowances for the true mean errors inherent in both standard and test devices and it is accepted that performance cannot be guaranteed at any particular pressure in any particular patient. In the present study, fewer than 33% of mean and diastolic, and only 10% of systolic recordings obtained with the Finapres conformed to these standards (figs 3–5). These proportions were not influenced by site of cuff placement (ipsilateral or contralateral), size of cuff (small, normal or large) or type of surgery. Whether or not ANSI standards formulated to evaluate devices using a cuff on the upper arm are applicable to a finger cuff non-invasive system, is open to question.

It is also interesting to contrast the performance of the Finapres with other non-invasive methods which have been tested against intra-arterial readings. From studies on the Korotkoff sounds [13], the oscillotonometer [14], and the Dinamap [15], it is apparent that the population regression equations produced by the Finapres (fig. 2) are superior in both intercept and slope, but have wider 95% confidence limits. Furthermore, the Finapres has less tendency to under-read high and over-read low arterial pressures. The oscillotonometer and Korotkoff sounds are subject to observer bias and results obtained from the studies undertaken probably are unlikely to be bettered. It is therefore difficult to deduce the true comparative performance in everyday practice. The Dinamap is an automated device and its 95% confidence limits on the population readings of ±16.4, ±16.1 and ±15.3 mm Hg for systolic, mean and diastolic pressures, respectively are considerably narrower than those obtained from the Finapres (fig. 2).

Consistency of performance of the Finapres was assessed during rapid changes in arterial pressure associated with induction of anaesthesia. Accurate continuous measurement of acute fluctuations in arterial pressure is the prime indication for invasive arterial monitoring in clinical practice. The Finapres did reflect accurately the rapid changes in intra-arterial pressure in most neurosurgical and major vascular surgery patients, but results were less satisfactory for cardiac patients. The pressure differences (systolic, diastolic and mean) between Finapres and invasive values showed matching fluctuations when the absolute pressure changed acutely (fig. 9). No consistent relationship could be demonstrated between absolute pressure and the magnitude of the pressure difference, although various patterns were identifiable. Occasionally, marked discrepancies in pressure difference occurred for no apparent reason.

Baseline drift

Finapres trend performance was assessed by comparison with intra-arterial pressure readings over several hours in patients undergoing neurosurgery. Systolic, diastolic and mean pressure differences exhibited matching baseline drift away from zero in just under 50% of recordings (fig. 9).

Trend analysis

Data were analysed to indicate the probability that a change in pressure recorded by the Finapres was accompanied by a change in invasive pressure in the same direction (but not necessarily of the same magnitude). This analysis suggested that diastolic and mean Finapres pressures were more likely than systolic pressure to change in phase with invasive pressure, for all patient groups (table II). The Finapres did follow changes in invasive pressure in 83% of all the comparisons made.

In conclusion, the 2300 Finapres non-invasive arterial pressure monitor displayed changes in intra-arterial pressure with a performance comparable to other non-invasive methods, but with considerable inter-individual variability in absolute pressure readings. Although the present study failed to identify clear relationships between patient or technical factors and the observed variability in performance of the Finapres, between- and within-patient differences in cardiac output and peripheral resistance may be important. Further investigation of the patient–cuff interface is also warranted. In view of these findings, the Finapres cannot be recommended at present as an alternative to invasive arterial pressure monitoring in clinical practice or clinical research. However, the Finapres does provide valuable information regarding trends in arterial pressure in patients in whom conventional non-invasive monitoring would be the method of choice, and has the advantage of displaying beat-to-beat recordings.

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COMPARISON OF THE FINAPRES AND DIRECT ARTERIAL PRESSURE MONITORING DURING PROFOUND HYPOTENSIVE ANAESTHESIA

H. A. AITKEN, J. G. TODD AND G. N. C. KENNY

SUMMARY

The Finapres was compared with direct intra-arterial pressure monitoring in 10 patients undergoing local resection of choroidal melanoma, an operation that requires a period of profound hypotension. Good agreement was recorded for systolic arterial pressure and heart rate over a range of pressures. However, agreement of mean and diastolic pressures was poor, with the Finapres tending to overestimate these values. In cases requiring profound hypotension, direct arterial pressure monitoring remains the method of choice.

KEY WORDS

Arterial pressure: measurement. Measurement techniques: invasive, non-invasive, Finapres.

During induced hypotensive anaesthesia, accurate and frequent measurement of arterial pressure is essential. As systolic arterial pressure is decreased, inadequate organ perfusion can occur. The risk may be minimized by knowledge of the precise perfusion pressure. Continuous monitoring of arterial pressure is therefore mandatory [1] and until recently this required cannulation of an artery. This is invasive and presents several hazards [2]. Although these adverse effects occur infrequently, it would be advantageous if an accurate, non-invasive method were available.

A new type of monitor has been produced commercially which allows continuous non-invasive arterial pressure monitoring using a finger cuff (Finapres 2300, Ohmeda). This device produces a calibrated arterial pressure wave based on the arterial volume-clamp method described by Penaz [3]. A cuff is placed round a finger and inflated to the pressure just less than that which causes the artery to collapse (zero transmural pressure). As the pressure in the artery increases, the volume changes. This is sensed by infra-red photoelectric receivers in the cuff, which immediately operates a servo pump, adjusting the cuff to maintain zero transmural pressure. Thus cuff pressure reflects intra-arterial pressure at all times. The instrument displays an arterial wave form and digital readings of heart rate, systolic, mean and diastolic arterial pressures.

We have compared the Finapres with direct arterial pressure monitoring in patients undergoing hypotensive anaesthesia for intraocular surgery. The patients studied were undergoing local resection of choroidal melanoma, which requires a period of profound hypotension with systolic arterial pressure maintained at about 40–50 mm Hg.

PATIENTS AND METHODS

We studied 10 patients undergoing local resection of choroidal melanoma. All patients eligible for this type of surgery [4] were considered suitable and informed consent was obtained. Hospital Ethics Committee approval was also received.

Before induction of anaesthesia, a 20-gauge cannula (Quikcath) was inserted in the right radial artery and direct arterial pressure monitoring commenced. The monitoring system comprised a saline-filled, single-use Utah transducer (American Edwards Laboratories) connected to

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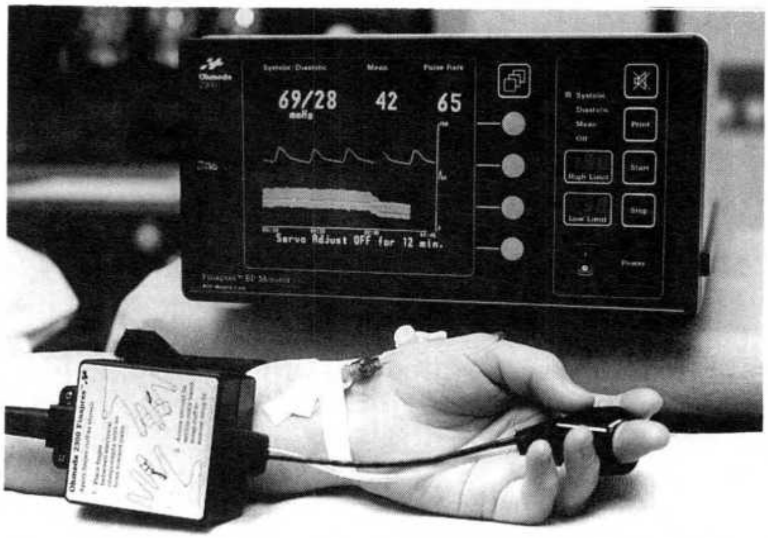

FIG. 1. The Finapres 2300 in use, showing arrangement of finger cuff and transducer. The arterial cannula for direct pressure monitoring is also seen.

a Datascope 2002 monitor. This system has a frequency response of 5–40 Hz, and was zeroed to atmosphere and calibrated using a 100-cm saline-filled manometer line before each case. The appropriate size of Finapres cuff was selected and applied to the middle finger of the same hand (fig. 1). The patient was positioned on the operating table and the height of both transducers checked to ensure that they were the same.

Anaesthesia was induced with thiopentone, and suxamethonium was given to facilitate tracheal intubation. The lungs were ventilated artificially with nitrous oxide and enflurane in oxygen, neuromuscular block being provided by incremental doses of tubocurarine. Hypotension was induced with a mixture of trimetaphan and sodium nitroprusside infused by volumetric pumps. A detailed description of the anaesthetic technique is provided by Todd and Colvin [5].

Systolic, mean and diastolic arterial pressures and heart rate were noted simultaneously from the screen display of both monitors at 10-min intervals, with the frequency of recording increased to 2-min intervals at times when arterial pressure was changing rapidly. Two anaesthetists were present so that the readings were truly simultaneous. In both machines, the averaging period of the values displayed on screen was 2 s.

The difference between each pair of readings was expressed as a percentage of the direct arterial pressure reading and frequency distributions plotted showing percentage differences for systolic, mean and diastolic pressures, and heart rate. In addition, for systolic pressure only, a plot was constructed showing the difference between each pair of readings against the direct arterial pressure reading [6].

The appearance of the cuff finger was noted at 1-h intervals during the measurement period and reviewed 24 h after operation.

RESULTS

Patient data are shown in table I.

The Finapres correlated reasonably well with direct arterial pressure for systolic arterial pressure, with more than 70 % of all values within 10 %

TABLE I. *Patient characteristics*

Patient No.	Sex	Weight (kg)	Cuff size	No. readings obtained
1	F	67	Large	48
2	F	58	Medium	35
3	M	72	Large	51
4	F	57	Large	38
5	M	75	Large	29
6	M	80	Large	33
7	F	76	Large	35
8	M	76	Large	34
9	M	91	Large	28
10	M	70	Large	30

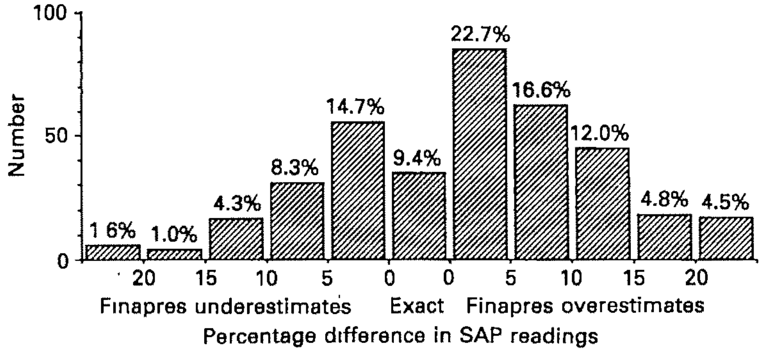

FIG. 2. Frequency distribution showing percentage differences of systolic pressure readings. The figure at the top of each column indicates the percentage of the total number of readings.

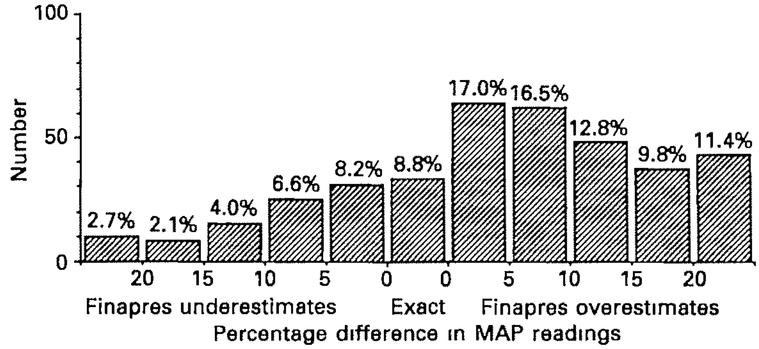

FIG. 3. Frequency distribution showing percentage differences of mean pressure readings. The figure at the top of each column indicates the percentage of the total number of readings.

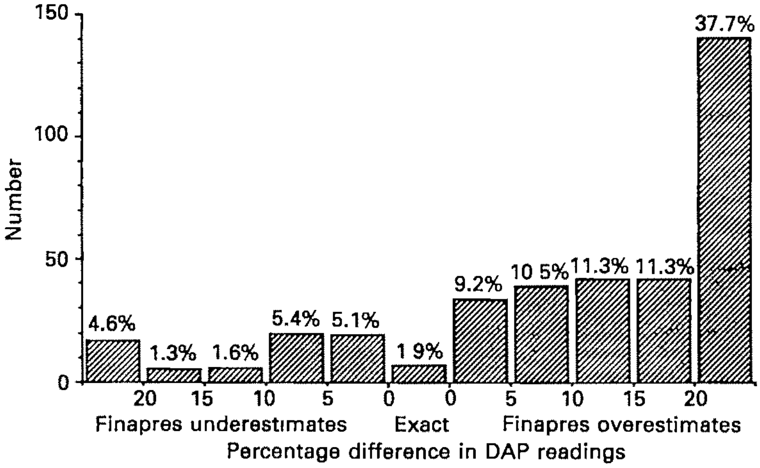

FIG. 4. Frequency distribution showing percentage differences of diastolic pressure readings. The figure at the top of each column indicates the percentage of the total number of readings.

(fig. 2). However, a small number of readings were found to over- or underestimate by more than 20%.

Mean and diastolic pressures displayed a poorer agreement. The Finapres showed a tendency to overestimate which was more marked for diastolic readings (figs 3, 4). In total, 67.6% of all mean values and 80% of all diastolic values were greater

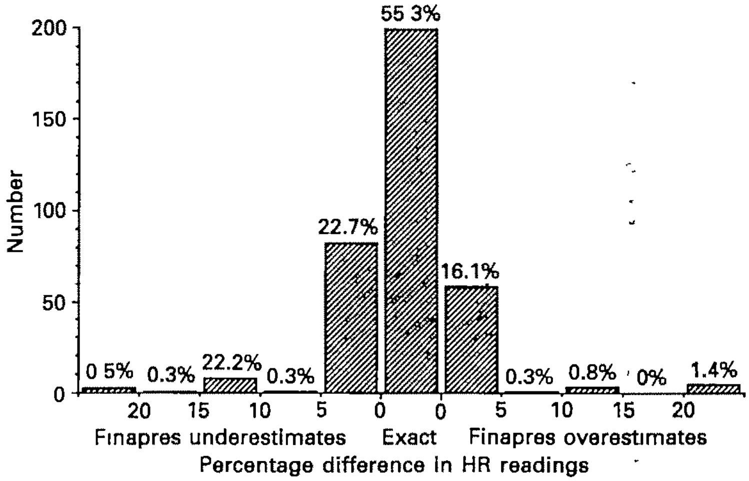

FIG. 5. Frequency distribution showing percentage differences of heart rate readings. The figure at the top of each column indicates the percentage of the total number of readings.

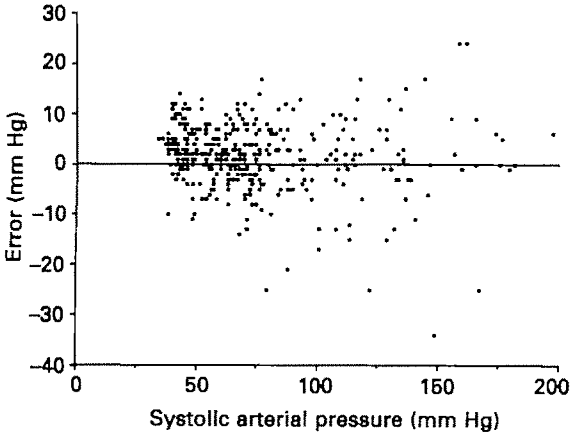

FIG. 6. Difference for each pair of values plotted against the direct arterial pressure reading (systolic pressure).

with the Finapres than the pressures measured directly.

There was excellent agreement between the two methods for heart rate (fig. 5).

The plot shown in figure 6 was constructed to compare the accuracy of the Finapres over the range of pressures seen. In general, the scatter of readings is clustered around the zero line, indicating good agreement. There is a trend towards wider spread at greater pressures, but as there were fewer values in this range, it is difficult to ascertain if this was a significant finding.

Although the cuff finger in many patients was noted to be cool and cyanosed during the procedure, this did not persist for longer than a few moments after cuff removal, and no sequelae related to the cuff were noted.

DISCUSSION

The operation for resection of choroidal melanoma takes between 200 and 300 min and requires a period of profound hypotension for 60–90 min, when the systolic pressure must be maintained in the range 40–50 mm Hg [5]. These patients therefore present the opportunity to evaluate arterial pressure monitoring devices in the clinical setting over a wide range of values.

The Finapres systolic pressure correlated well with direct arterial pressure monitoring in this group of patients over the whole range of pressures seen. However, there were a small number of values widely different from direct arterial pressure values, which could, on occasion, be misleading.

The results for mean and diastolic pressures are less acceptable. Of particular concern was the tendency to overestimate, which is more hazardous than underestimating, as the clinician may attempt to reduce arterial pressure further, and in this particular procedure, this might result in cerebral or coronary perfusion becoming compromised.

The Finapres might be expected to perform well in this group of patients, in whom hypotension had been induced by peripheral vasodilatation. These are ideal conditions for this monitor, which some authors suggest may perform less well in patients with peripheral vasoconstriction [7]. The trend noted in figure 6, which may suggest poorer agreement at greater systolic pressures, was obtained in the early stages of each operation, before commencement of trimetaphan and nitroprusside infusions.

At the extremely small pressures required for ischaemic choroidal dissection, the margins of error are small and we feel that invasive monitoring is still indicated. However, in moderate induced hypotension the continuous reading provided by the Finapres may prove more useful than automated non-invasive pressure monitors which work on the oscillotonometric principle and have a minimum cycle time of 30–60 s [8]. The role of the Finapres may be to improve continuity of monitoring by replacing this type of machine, rather than superseding invasive pressure monitors.

ACKNOWLEDGEMENTS

The Medical Physics Department of The Western Infirmary provided invaluable assistance with the technical aspects of this study. The Finapres was loaned by Ohmeda.

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PHARMACOKINETIC MODEL DRIVEN INFUSION OF PROPOFOL IN CHILDREN

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SUMMARY

A computer controlled infusion device for propofol was used to induce and maintain general anaesthesia in 20 children undergoing minor surgical procedures. The device was programmed with an adult pharmacokinetic model for propofol. During and after anaesthesia, blood samples were taken for measurement of propofol concentrations and it was found that the values obtained were systematically overpredicted by the delivery system algorithm. New pharmacokinetic microconstants were derived from our data which reflected more accurately the elimination and distribution of propofol in a prospective study involving another 10 children.

KEY WORDS

Anaesthesia: paediatric. Anaesthetics, intravenous: propofol. Pharmacokinetics: computer model.

The use of i.v. agents to maintain anaesthesia has become increasingly popular since the introduction of propofol. Several manual infusion schemes have been proposed for use in adults, based either on the concept of minimum infusion rate [1] or on approximations to computer generated infusion regimens [2]. Alternatively, delivery may be effected automatically by a pharmacokinetic model driven computer controlled device [3, 4]. This latter approach allows anaesthetic drugs to be administered to a theoretical target plasma concentration calculated mathematically by the delivery system algorithm.

Hitherto, experience with these systems has been confined to adult patients. There is considerable interest in the use of propofol in children, particularly within the context of day-case anaesthesia. Browne, Wolf and Prys-Roberts have proposed recently a manual infusion regimen for paediatric use of propofol and alfentanil [5]. They found the resultant anaesthesia to be satisfactory, providing the increased requirement for propofol in this age group was taken into account. Recent studies of the pharmacokinetic behaviour of propofol after administration of a bolus [6, 7] have suggested a disparity in pharmacokinetic behaviour of the drug between adults and children, which would account for at least part of this increased requirement.

In this study, we report the use in 20 healthy children of a computer controlled infusion system for propofol [4] which used initially an adult pharmacokinetic model described previously. The principal objective of the study was to derive new pharmacokinetic microconstants which more accurately described the elimination and distribution of propofol during infusion anaesthesia in children.

PATIENTS AND METHODS

The infusion system consisted of a Psion II computer interfaced with the Ohmeda 9000 infusion device [8]. We retained the adult three-compartment model used previously [4], describing the pharmacokinetics of propofol [9] with the microconstants of rate of transfer between the three compartments as shown in table I. It was necessary to increase the maximum predicted target plasma concentration of propofol to 15 $\mu g\ ml^{-1}$ (originally 10 $\mu g\ ml^{-1}$ in the adult system). This was to allow for the greater

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TABLE I. *Adult pharmacokinetic variables for propofol* [9]. ** Obtained from our own pilot studies*

Vc	228 ml kg^{-1}*
k_{10}	0.119 min^{-1}
k_{12}	0.112 min^{-1}
k_{13}	0.0419 min^{-1}
k_{21}	0.055 min^{-1}
k_{31}	0.0033 min^{-1}

requirement for propofol in children. Adjustments to the pharmacokinetic variables were made solely on the basis of body weight. The Ohmeda 9000 infusion pump was set at a maximum infusion rate of 1200 ml h^{-1}. Precise details of the theoretical blood propofol profile, together with the infusion regimen delivered to each patient, were recorded automatically on the Psion datapacks and these were stored for subsequent computer analysis.

For the first part of the study, we studied 20 children (ages 1–12 yr, ASA grades I or II) presenting for inpatient general surgical or urological procedures (group 1). In the second prospective part of the study, we studied another 10 children (ages 1–9 yr) (group 2). Ethics Committee approval was obtained and written informed consent was given by each patient's parents or guardian.

Anaesthetic technique

Premedication consisted of oral temazepam elixir 0.3 mg kg^{-1} or trimeprazine elixir 2 mg kg^{-1} 1 h before operation. At the same time, EMLA cream was applied under an occlusive dressing to the dorsum of each hand. In the anaesthetic room, a 22-gauge cannula was inserted to a vein in the dorsum of the child's hand and connected to the infusion pump via a 200-cm extension. Immediately before induction of anaesthesia, the child's weight was entered into the Psion, as was the selected theoretical target blood concentration of propofol. Anaesthesia was induced with the pump operating at maximal flow rate (1200 ml h^{-1}), delivering propofol to the desired theoretical target plasma concentration. Anaesthesia was supplemented with 66% nitrous oxide in oxygen via a facemask or laryngeal mask. Analgesia was provided by an appropriate regional nerve block (which consisted of either an ilio–inguinal nerve or caudal block with 0.25% bupivacaine 0.5 ml kg^{-1}). All patients were allowed to breathe spontaneously throughout the procedure and each was monitored with a pulse oximeter, automated non-invasive arterial pressure cuff and electrocardiograph and the quality of anaesthesia was assessed by the supervising anaesthetist according to the presence or absence of either patient movement or cardiorespiratory changes.

Peripheral venous blood samples (maximum 1 ml kg^{-1}) were collected from a large forearm vein on the side of the body contralateral to the site of infusion for measurement of whole blood concentration of propofol according to the method of Plummer [10], the only modification being that the final residuum was analysed by gas–liquid chromatography rather than high pressure liquid chromatography. The between-batch coefficient of variation of the assay was 4.9% at 1 μg ml^{-1} and 2.1% at 10 μg ml^{-1}. The limit of detection was 50 ng ml^{-1}. The calibration graphs were linear over the range 50–20000 ng ml^{-1}.

During operation, the target blood concentration was adjusted to a value appropriate to maintain adequate anaesthesia as judged clinically by the supervising anaesthetist. At the end of the operation, the infusion pump was switched off and further sampling was perfomed until eye-opening was observed. During this recovery phase, the system continued to calculate theoretical blood concentration.

Computer analysis

Throughout the study, measured blood concentrations of propofol (Cp) were compared with the corresponding delivery system predicted value. The prediction error was calculated for each data point, this being defined as [11, 12]:

Prediction error

$$= \frac{Cp\,(\text{measured}) - Cp\,(\text{predicted})}{Cp\,(\text{predicted})} \times 100$$

Bias is defined as the mean prediction error and is taken in these circumstances to be a measure of the systematic tendency of the system to underestimate the measured concentration of blood propofol. That is to say, if bias has a positive value, then the measured value is, on average, greater than the system prediction and *vice versa*. Precision is defined as the mean value of the sum of individual absolute values of prediction error and is a measure of the degree of scatter of the data about the line of perfect prediction.

Computer analysis of the data for each individual was performed using an iterative weighted least squares regression program which minimized the total squared prediction error for each patient. In each case, all microconstant systems producing a fit with a consequent value of bias for each individual within 10% were stored on computer disc. The data obtained for the entire population were subjected to a second analysis in which each individual's file of microconstant solutions was applied systematically to all the patient profiles in the study in such a way as to select the microconstant system which was calculated to produce the minimum population bias.

RESULTS

Figure 1 illustrates the course of a typical anaesthetic administered to a 22.5-kg child (aged 7 yr) undergoing herniotomy using the computer aided infusion device. Anaesthesia was induced by selecting an initial theoretical target concentration of 14 μg ml^{-1}. Thereafter, the target could be reduced to 12 μg ml^{-1} without deterioration in the operating conditions, and this target value was maintained for the remainder of the operating time. The anaesthetist retained at all times the option of increasing or decreasing the theoretical target blood concentration according to his or her clinical impression of the quality of anaesthesia. At the termination of surgery, the pump was switched off and the patient transferred to the recovery room, where the device calculated the theoretical decay of propofol concentration in the patient's blood until eye opening was observed. In figure 1, the measured values of blood propofol are overlaid on the system record of the theoretical propofol profile and it can be seen that, in this individual, the delivery system consistently overpredicted the measured blood concentration of propofol.

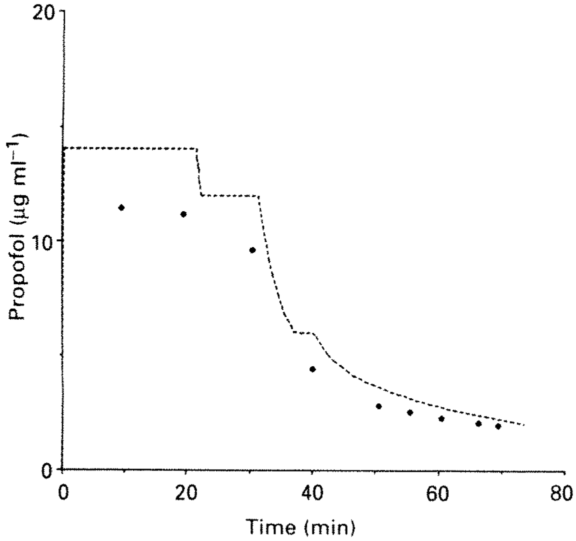

FIG. 1. Predicted and measured blood concentrations of propofol during anaesthesia in a 22.5-kg patient (age 7 yr). The dotted line represents predicted values; individual points are measured values.

TABLE II. *Patient characteristics (mean (SD) [range])*

	Group 1	Group 2
n	20	10
Age (yr)	4.8 [2–10]	4.9 [1–9]
Weight (kg)	18.3 (4.4) [12–28.8]	17.4 (4.9) [12.7–30]

For the population in the first study (table II), each measured blood value of propofol was compared with its corresponding delivery system prediction and the relationship obtained is displayed in figure 2. These results were plotted in the form of percentage error *vs* predicted concentration (fig. 3). It may be seen from this figure that the majority of the data points lie below the line of zero prediction error (the line of perfect prediction). The population mean prediction error (bias) was calculated to be −18.5% and the corresponding value for precision obtained was 25.4%. Hence it was concluded that the delivery device systematically overpredicted the measured values of blood propofol. The most likely reason for this finding is that, compared with adults, children have different pharmacokinetics for handling the drug, and a revised pharmacokinetic model is required to effect more accurate delivery of propofol in the paediatric population under conditions of infusion anaesthesia. In order to derive such a pharmacokinetic model, computer analysis of the data for each individual was performed using the methodology described in the Computer Analysis section.

The microconstant systems which gave the best fit for each individual are detailed in table III. The data obtained for the entire population were then subjected to a second analysis in which each individual's file of microconstant solutions was applied systematically to all the patient profiles in the study in such a way as to select the microconstant system which was calculated to produce the smallest population bias. In this way,

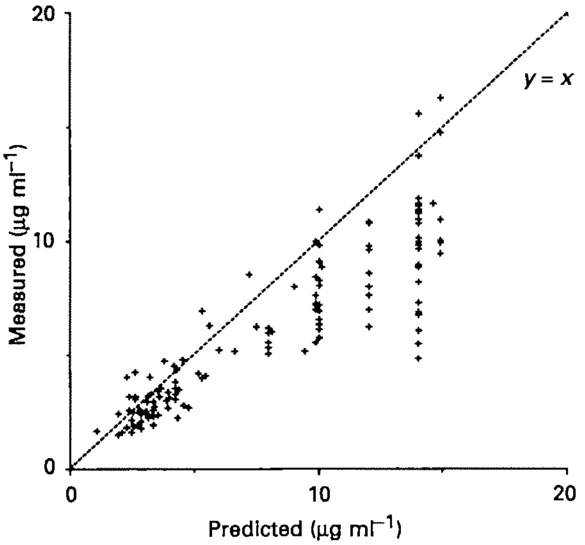

FIG. 2. Comparison of measured and predicted blood concentrations of propofol for the study population. The dashed line is the line of identity ($y = x$).

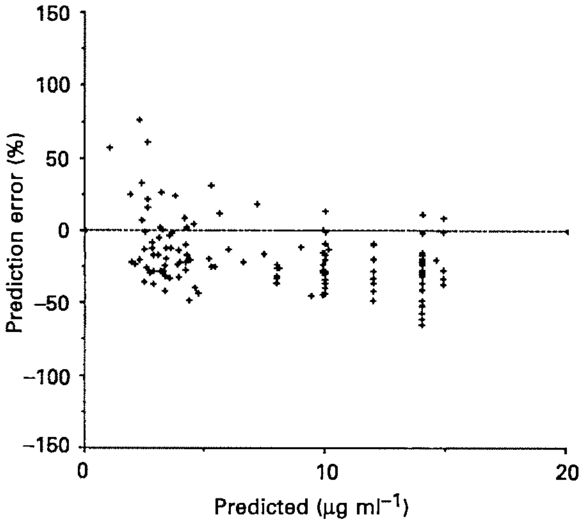

FIG. 3. Comparison of percentage prediction error and predicted values.

a new microconstant system producing a study population bias of 0.9% (precision 20.1%) was recorded (table IV). This value of bias for the new microconstant system is determined on the basis of a new calculated predicted value relating to each experimentally obtained measured blood value. The relationship between each of these new calculated predictions with each of its related measured blood values is displayed in figure 4. In figure 5, each new prediction error is related to its new predicted value. Comparison of this plot with that in figure 3 reveals that the data points are now distributed about the line of zero prediction error (the line of perfect prediction) in such a way that the mean prediction error (bias) is almost zero whereas previously, on the basis of the adult

TABLE III. *Individual best fit pharmacokinetic variables. In all patients* $k_{31} = 0.0033$ *min*$^{-1}$. *The value of* k_{31} *was not iterated in the computer analysis, as simulation revealed that substantial variation of this microconstant made little difference to the prediction obtained and that non-iteration of* k_{31} *decreased the program run greatly to acceptable times*

Patient no.	Age (yr)	Weight (kg)	Vc (ml kg^{-1})	k_{10} (min^{-1})	k_{12} (min^{-1})	k_{13} (min^{-1})	k_{21} (min^{-1})
1	5	21.6	343	0.08	0.085	0.042	0 03
2	5	18	371	0.12	0.114	0.021	0.08
3	7	20	314	0.10	0.17	0.021	0.04
4	10	25.6	257	0.08	0.17	0.021	0.04
5	4	16.6	371	0.1	0.114	0 042	0.04
6	7	22.5	371	0.08	0.085	0.031	0.03
7	3	15.2	343	0.1	0.057	0 021	0.04
8	5	16.2	371	0.12	0.057	0.021	0.03
9	3	15.8	343	0.08	0.142	0 021	0.03
10	2	14.5	257	0.1	0 17	0.031	0.04
11	2	12	343	0 16	0 17	0 042	0.05
12	4	20	343	0 1	0.17	0.042	0.05
13	7	28 8	371	0.08	0.142	0.031	0 03
14	5	21	286	0.14	0.114	0.063	0.05
15	9	17.5	343	0.12	0 142	0.05	0.07
16	3	16.2	343	0.08	0.057	0.021	0.03
17	3	12.7	343	0.18	0.171	0.021	0.08
18	4	15.7	371	0.08	0 085	0 063	0 05

TABLE IV. *Derived pharmacokinetic microconstants for paediatric population (group 1), and comparison of bias and precision (95% confidence limits) obtained by computer simulation using these microconstants with values obtained experimentally using the adult pharmacokinetic delivery system*

Derived microconstant		Bias (%)	Precision (%)
Vc	343 ml kg^{-1}	Adult system	
k_{10}	0.1 min^{-1}	−18.5 (−14.8 to −22.6)	25.4 (22.8–27.8)
k_{12}	0.0855 min^{-1}		
k_{13}	0.021 min^{-1}	Paediatric simulation	
k_{21}	0.033 min^{-1}	0.9 (−4 to 5.7)	20.1 (17.6–24.2)
k_{31}	0.0033 min^{-1}		

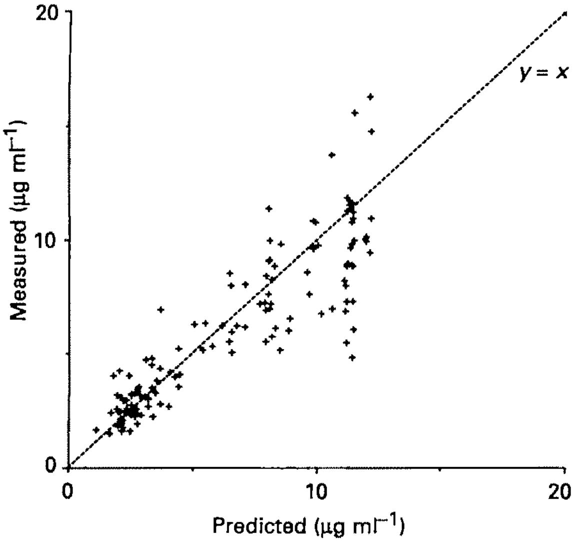

FIG. 4. Comparison of measured and predicted blood concentrations of propofol for the study population. The predicted values are derived by pharmacokinetic simulation using the derived paediatric pharmacokinetic parameters for propofol. Dotted line represents the line of identity ($y = x$).

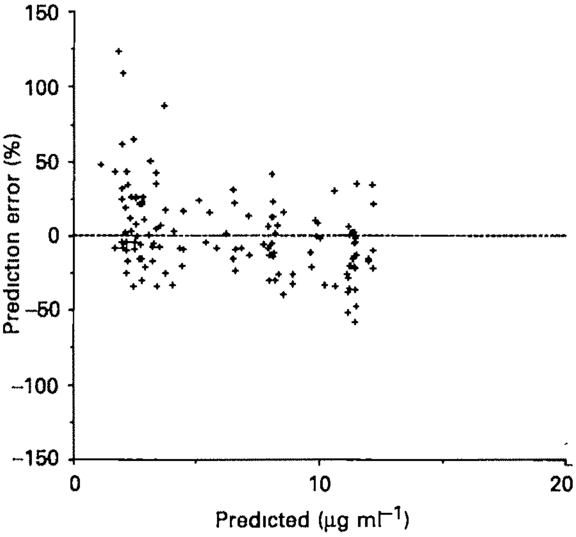

FIG. 5 Comparison of percentage prediction error and new predicted values obtained by pharmacokinetic simulation using the derived paediatric pharmacokinetic parameters for propofol.

pharmacokinetic model, the data points generally tended to lie well below the line (resulting in negative bias). In figure 6, a pharmacokinetic simulation program has been used to predict the effect (using the new pharmacokinetic model) on blood concentration of propofol of the infusion regimen administered to the patient referred to in figure 1. The infusion regimen is a function of the adult pharmacokinetic microconstants used in the original delivery system and the postulated patient model, into which the drug is delivered, is governed by the new derived microconstants detailed in table IV. The new computer prediction has been overlayed on the data displayed in figure 1. It can be seen from this figure that the new paediatric pharmacokinetic model produces a predicted concentration profile for propofol that fits more closely the measured blood values obtained for this particular patient.

In order to test the new paediatric pharmacokinetic model prospectively, a second study was performed in the patients in group 2 (table II). In this second study, the computer controlled propofol infusion system was programmed with the revised paediatric microconstants. As before, measured blood concentrations of propofol were compared with their corresponding predicted values calculated by the delivery system algorithm. Figure 7 shows the relationship between measured and predicted values for the entire prospective study population and figure 8 shows the distribution of prediction errors in relation to their predicted values. The bias of the revised

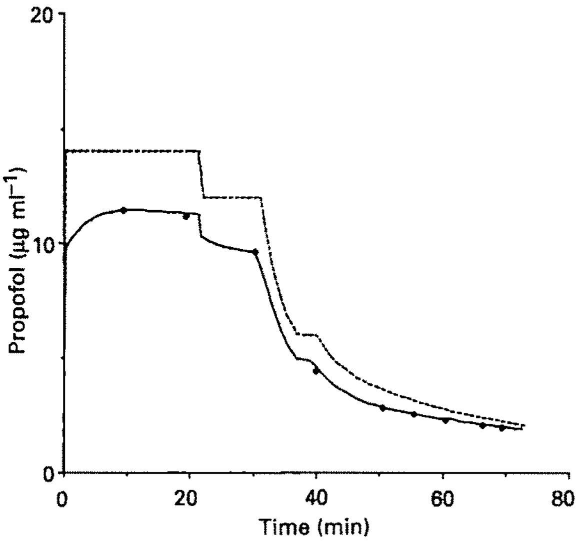

FIG. 6. Predicted and measured blood concentrations of propofol for the patient referred to in figure 1, the predicted values in this case calculated by computer pharmacokinetic simulation using the derived paediatric parameters. The computer generated profile (solid line) is superimposed on figure 1.

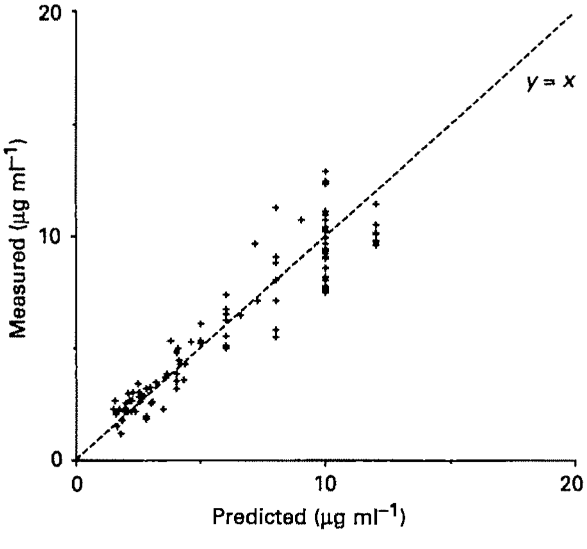

FIG. 7. Comparison of measured and predicted values for the prospective study population (group 2). The computerized infusion system was programmed with the revised paediatric microconstant system. Dotted line represents the line of identity ($y = x$).

delivery system was calculated to be 2.8% and the corresponding value of precision was 16.2%. It can be seen that, prospectively, the revised paediatric microconstant system gave a relationship between measured and predicted values of blood propofol which was superior to that obtained using the adult microconstant system used in the initial study and which compared closely to the relationship predicted by computer simulation using the revised paediatric microconstant system.

DISCUSSION

In this report, we have described the use of a computer controlled propofol infusion device to maintain general anaesthesia in a population of children undergoing minor general surgical procedures. At the commencement of this study, no information was available describing the pharmacokinetics of propofol in young children. The device was therefore programmed with adult pharmacokinetic microconstants and it was observed that the theoretical blood concentration of propofol was attained only rarely on direct measurement of drug concentration in the patients' blood. The delivery device was observed to overpredict systematically the measured blood concentration of propofol (bias = −18.5%). The major objective of this study was to derive from

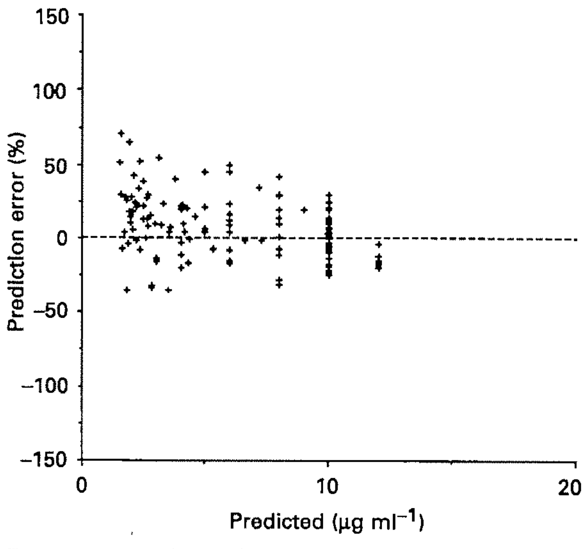

FIG. 8. Comparison of percentage prediction error and predicted values of blood concentrations of propofol corresponding to the data presented in figure 7. Dotted line represents the line of zero prediction error.

TABLE V. *Pharmacokinetic variables for propofol derived after the administration of a single dose* [6]

Vc	722 ml kg^{-1}
k_{10}	0.0509 min^{-1}
k_{12}	0.112 min^{-1}
k_{13}	0.0195 min^{-1}
k_{21}	0.0454 min^{-1}
k_{31}	0.00143 min^{-1}

these measurements of blood propofol a new set of pharmacokinetic microconstants which more accurately describes the elimination and distribution of the drug in children during infusion anaesthesia (bias = 0.9%) (table IV). The derived paediatric pharmacokinetic system was tested prospectively in a second study population and this resulted in a bias of 2.8%.

The precision calculated when the revised pharmacokinetic microconstants are applied to the data in group 1 was 20.1%, which differs little from the value obtained originally when the adult system was applied. Indeed, it proved impossible by computer modelling to construct a single pharmacokinetic model for the study population which resulted in a precision of much less than this value. In the prospective study, a value for precision of 16.2% was obtained. It is likely that the observed values of precision that we have obtained are a consequence of heterogeneity of pharmacokinetic handling within our study populations and that precision could be improved only by creating multiple models within the study population to account for pharmacokinetic variability.

The volume of the central compartment (Vc) of the new paediatric model was calculated to be 343 ml kg^{-1}, which is approximately 50% greater than the value used in the adult pharmacokinetic model (228 ml kg^{-1}). The clearance of the drug, which is the product of Vc and k_{10}, is calculated to be 34.30 ml kg min^{-1}, compared with an adult value of 27.36 ml kg min^{-1}.

Saint-Maurice and colleagues [6] have reported information on the pharmacokinetic behaviour of propofol in a population of 10 children, aged 4–7 yr, based on the administration of a bolus dose of propofol at induction (table V). They reported a substantially greater value for Vc in children (722 ml kg^{-1}) compared with adults, but a broadly similar value of clearance (30.6 ml kg^{-1} min^{-1}). We used a pharmacokinetic simulation program to test the response of Saint-Maurice's microconstant system to the infusion profiles delivered to the patients in our study. We found that this microconstant system systematically underpredicted the measured values of blood propofol obtained from the patients in our study (bias = 33.9% (95% confidence limits (CL) 27.1–40.6); precision = 40% (95% CL 35.3–46.4). We concluded, therefore, that the microconstants derived by Saint-Maurice and colleagues were unsuitable for describing the elimination and distribution of propofol in children during infusion anaesthesia. It is possible that this result derives from the difficulty in describing the initial distribution phase of the drug following bolus administration, because of the effects of inadequate mixing immediately after administration and because of difficulties inherent in the necessity for rapid sampling [13, 14].

It was found during the course of this study that substantially greater theoretical target concentrations of propofol were required to maintain adequate anaesthesia in children than observed previously in the adult population [4]. It was frequently necessary to achieve a theoretical target concentration of 14 μg ml^{-1} in order to achieve satisfactory induction, whereas in adults a theoretical target of 4–6 μg ml^{-1} was usually adequate. This discrepancy is explained in part by the differences in propofol pharmacokinetics of the two populations and in part by the consideration that no opioid agent was used in our paediatric study, analgesia being provided instead by a local block.

The principal consequences for an infusion scheme using our newly derived paediatric pharmacokinetic microconstant system for propofol are that, for a given target, the size of the initial loading bolus is increased by approximately 50% compared with the adult system and the maintenance infusion thereafter is increased by approximately 25% at equilibrium.

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DISPOSITION OF PROPOFOL AT CAESAREAN SECTION AND IN THE POSTPARTUM PERIOD

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SUMMARY

We have compared the pharmacokinetics of a bolus dose of propofol 2 mg kg^{-1} in eight patients undergoing Caesarean section with those in eight postpartum patients undergoing sterilization by mini-laparotomy. The Caesarean section group had a total body clearance of (median) 31.5 (range 24.4–53.3) ml min^{-1} kg^{-1}, apparent volume of distribution at steady state 5.10 (2.46–6.61) litre kg^{-1} and mean residence time 161 (52.3–251) min; values for the postpartum group were 33.8 (21.5–47.2) ml min^{-1} kg^{-1}, 5.17 (3.47–8.09) litre kg^{-1} and 163 (92.3–238) min, respectively. The 95% confidence interval for the umbilical venous to maternal venous ratio of propofol at delivery was 0.62–0.86. Plasma protein binding studies showed there was less unbound propofol in maternal plasma (1.28–2.29%) compared with umbilical plasma (2.08–3.88%) ($P < 0.01$). Neonatal concentrations of propofol were greater than maternal concentrations at 2 h and were in the range 0.05–0.11 µg ml^{-1} at 4 h.

KEY WORDS

Anaesthesia: obstetric. Anaesthetics, intravenous: propofol. Pharmacokinetics: propofol, pregnancy, puerperium.

Propofol has been used for induction and maintenance of anaesthesia during Caesarean section because of the potential for rapid maternal and neonatal recovery [1–6]. Some studies using larger doses of propofol have reported lower Apgar and neurobehavioural assessment scores in neonates [1, 7]. Concentrations of propofol in neonatal heel prick blood samples 2 h after delivery were small [4], but there are no data on the protein binding or neonatal elimination of propofol.

The total body clearance of propofol was found to be increased in patients undergoing Caesarean section compared with non-pregnant patients undergoing laparoscopic operations [8]. The increase in clearance may have been caused by removal of fetal and placental tissues at operation, or by the physiological changes of pregnancy, with increased cardiac output or enzyme induction leading to increased metabolism of propofol.

Women in the immediate postpartum period possess many of the physiological changes of pregnancy [9, 10], but do not have the blood loss, fluid replacement and loss of fetal compartment that complicate pharmacokinetic analysis in women undergoing Caesarean section. A pharmacokinetic study of propofol in postpartum patients may provide clues to determine the cause of the increased clearance found at Caesarean section.

PATIENTS AND METHODS

The study was approved by the Research Ethics Committee of the Chinese University Faculty of Medicine and informed consent was given by all patients. We studied eight healthy patients with uncomplicated, singleton pregnancies for elective Caesarean section and eight ASA I patients, 2–3 days postpartum, for sterilization by mini-laparotomy tubal ligation.

In both groups, ranitidine 150 mg was given the night before and on the morning of surgery, with 0.3-mol litre^{-1} sodium citrate 30 ml given 15 min

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before operation. Routine monitoring included pulse oximetry and end-tidal capnography. Patients underwent preoxygenation for 3 min before rapid sequence induction of anaesthesia with propofol 2 mg kg^{-1} over 20 s followed by suxamethonium 1.5 mg kg^{-1}. After tracheal intubation, neuromuscular block was maintained with atracurium 0.5 mg kg^{-1}. In the Caesarean section group, anaesthesia was maintained with 50% nitrous oxide and 1% enflurane in oxygen. At delivery, the inspired gas mixture was changed to 70% nitrous oxide and 0.5% enflurane in oxygen, an oxytocin infusion was started and morphine 0.2 mg kg^{-1} given i.v. The postpartum patients received 70% nitrous oxide and 1% enflurane in oxygen throughout the operation and no opioid drugs were administered.

Venous blood samples (2 ml) were taken before induction and at 2, 4, 6, 8, 10, 20, 30, 60, 120, 240, 360, 480 and 600 min in both groups. Additional maternal venous (MV), umbilical venous (UV) and umbilical arterial (UA) blood samples were taken at delivery in the Caesarean section group. Venous blood samples were taken from the neonate at times that coincided with the maternal samples. Neonatal blood samples were taken at 30, 60 and 120 min ($n = 4$), 30, 60 and 240 min ($n = 2$) or 30, 120 and 240 min ($n = 2$). Blood concentrations of propofol were measured by high pressure liquid chromatography with fluorescence detection as described previously [8]. The blood concentration–time profiles of propofol were analysed according to a model independent method [11] to give the following pharmacokinetic variables: apparent volume of distribution at steady state (V^{ss}), mean residence time, elimination half-life ($T_{\frac{1}{2}}^{\beta}$) and total body clearance. Non-compartmental analysis was used because the removal of fetal and placental tissues at Caesarean section would have an unpredictable effect on a compartmental model [8].

Protein binding studies were carried out by equilibrium dialysis using a Dianorm apparatus (Diachem AG, Zurich, Switzerland). Plasma samples (1 ml) containing propofol were dialysed against 0.067-mol $litre^{-1}$ phosphate buffer made isotonic with sodium chloride 1 ml (pH 7.4) without propofol in Teflon dialysis chambers separated by a Spectrapor dialysis membrane. An equilibrium between the two sides of the dialysis membrane was attained within 4 h at 37 °C with a rotation speed of 12 r.p.m. The samples were analysed for propofol content to give the percentage of protein bound and free propofol in plasma.

Neonates were assessed by cord blood-gas analysis, Apgar scores at 1 and 5 min and Neurologic and Adaptive Capacity Scores (NACS) at 15 min, 2 h and 24 h.

Between group comparisons were made using the Mann–Whitney test for the derived pharmacokinetic variables and the unpaired t test for measured data. The paired t test was used to compare maternal with neonatal concentrations of propofol. Results are expressed as mean (SD); $P < 0.05$ was considered significant.

RESULTS

The patients in the Caesarean section group (27.4 (4.3) yr and 72.5 (9.1) kg) were heavier than those in the postpartum group (30.8 (4.3) yr and 62.0 (11.8) kg) ($P < 0.05$). Duration of anaesthesia was shorter in the postpartum group (30.2 (8.7) min) compared with the Caesarean section group (43.1 (6.2) min) ($P < 0.01$).

The concentration of propofol declined with time, but secondary peaks were observed in 11 patients shortly after the end of anaesthesia (fig. 1). Propofol was not detectable at 600 min in three patients in the Caesarean section group. Pharmacokinetic variables were similar between the groups (table I).

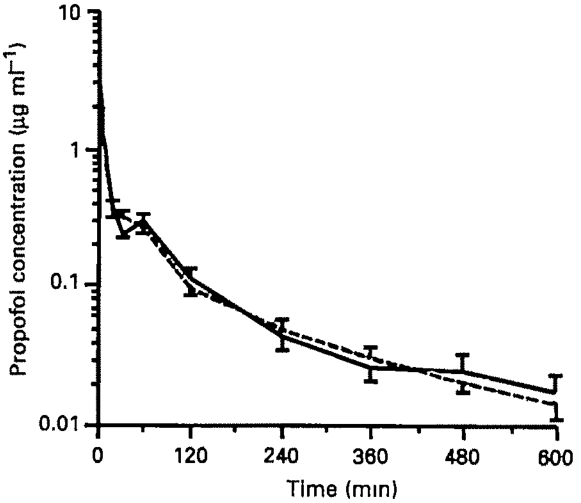

FIG. 1. Mean (SEM) venous blood propofol concentrations after induction of anaesthesia with propofol 2 mg kg^{-1} in eight patients undergoing Caesarean section (——) and eight patients undergoing postpartum sterilization (---).

TABLE I. *Median (range) pharmacokinetic variables for patients undergoing Caesarean section or postpartum sterilization.* V^{ss} = *Volume of distribution at steady state*; Cl = *clearance*; *MRT = mean residence time*; $T_{\frac{1}{2}}^{\beta}$ = *elimination half-life*

	Caesarean section	Postpartum sterilization
V^{ss} (litre kg^{-1})	5.10 (2.46–6.61)	5.17 (3.47–8.09)
Cl (ml kg^{-1} min^{-1})	31.5 (24.4–53.3)	33.8 (21.5–47.2)
MRT (min)	161 (52.3–251)	163 (92.3–238)
$T_{\frac{1}{2}}^{\beta}$ (min)	170 (60.7–275)	211 (117–345)

TABLE II. *Total whole blood concentration of propofol and plasma protein binding data from maternal vein (MV), umbilical vein (UV) and umbilical artery (UA) at delivery. CI = Confidence interval*

	Mean	SD	Range	95% CI
MV (μg ml^{-1})	0.79	(0.24)	0.54–1.21	
UV (μg ml^{-1})	0.58	(0.20)	0.33–0.84	
UA (μg ml^{-1})	0.60	(0.14)	0.47–0.89	
UV/MV	0.74	(0.14)	0.50–0.92	0.62–0.86
UA/UV	1.10	(0.28)	0.77–1.51	0.86–1.33
Unbound propofol (%)				
UV plasma	3.12	(0.74)	2.08–3.88	
MV plasma	1.75	(0.36)	1.28–2.29	

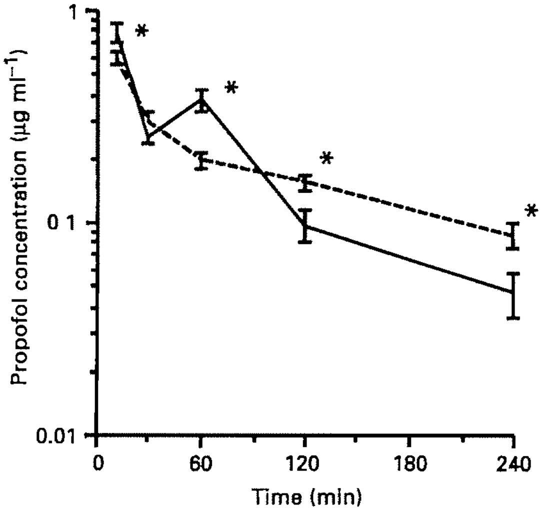

FIG. 2. Mean (SEM) propofol concentrations in mothers (——) and neonates (----) at delivery and at 30, 60, 120 and 240 min after induction of anaesthesia for Caesarean section. $^*P < 0.05$ between groups.

Maternal and umbilical concentrations of propofol at delivery are shown in table II. There was a higher percentage of unbound propofol in umbilical plasma (3.12 (0.74)%) compared with maternal plasma (1.75 (0.36)%) ($P < 0.01$). There was insufficient blood for propofol assay in three neonatal samples, so the available data were obtained at 30 min ($n = 8$), 60 min ($n = 4$), 120 min ($n = 5$) and 240 min ($n = 4$). Maternal concentrations were always greater than umbilical venous concentrations at delivery, but by 2 h all neonatal concentrations were greater than the corresponding maternal concentrations (fig. 2) ($P < 0.05$).

Neonates were of 37–39 weeks gestation with birth weights 2.6–3.9 kg. Induction to delivery times were in the range 8.7–12.3 min; umbilical blood-gas analysis, Apgar scores and NACS were all satisfactory. The median (range) NACS at 15 min was 33 (30–35). There were no anaesthetic or obstetric complications.

DISCUSSION

Pharmacokinetic variables for propofol in patients undergoing Caesarean section were similar to those in patients during the immediate postpartum period. There was reduced protein binding of propofol in fetal plasma compared with maternal plasma. The concentration of propofol in the neonate exceeded that in the mother by 2 h and this suggested that the elimination of propofol was slower in the neonate than in the mother.

Studies in postpartum patients may indicate the effect of late pregnancy on the pharmacokinetics of some drugs, even though these patients are no longer pregnant. Postpartum patients retain many of the physiological changes of pregnancy, some of which take up to 6 weeks to return to normal [9, 10]. In contrast with the pregnant patient at term, the puerperal patient no longer carries the fetus and placenta; however, these tissues contribute little to overall maternal drug metabolism and the absence of fetal and placental tissues should not have a significant effect on calculations of maternal V^{ss} if pharmacokinetic variables are corrected for body weight and if the V^{ss} is large for the drug being studied.

The puerperal period itself is also of interest, as patients may require anaesthesia and changes in the duration of action of some drugs have been reported. The decrease in pseudocholinesterase activity is greatest at this time [12] and the clinical duration of action of vecuronium was found to be longer in postpartum patients compared with non-pregnant patients [13].

The values for V^{ss} and $T_{\frac{1}{2}}^{\beta}$ in the Caesarean section group are within the range of that found in other studies, but greater than that reported in our previous study [8] because the sampling period was longer in the present study [14]. The effect of different sampling periods generates uncertainty regarding the true pharmacokinetic values, with one study reporting a mean V^{ss} of 771 litre and a $T_{\frac{1}{2}}^{\gamma}$ of 674 min in young patients when a sampling time of 24 h was used [15]. However, this terminal $T_{\frac{1}{2}}^{\gamma}$ is not directly comparable with our $T_{\frac{1}{2}}^{\beta}$ because the variables were calculated by different methods. The $T_{\frac{1}{2}}^{\gamma}$ relates also to very small, clinically insignificant concentrations of propofol being redistributed back to the central compartment after a single bolus dose, and the effect of this terminal portion on the area under the concentration–time curve and subsequent calculations of clearance would be very small. A change in volume of distribution during pregnancy affects calculations of elimination half-life, so it is a less reliable index of the rate of metabolism and clearance is a more meaningful indicator [16].

The mean values for clearance of propofol in non-pregnant subjects are more consistent among studies, including those with long sampling times, but less than that found in our peripartum patients. The clearance in the non-pregnant group in our previous study (mean 1.57 litre min^{-1}) [8] was less than that in the Caesarean section group in this study ($P < 0.05$), but not significantly less than the clearance in the postpartum group ($P = 0.16$). Unfortunately, differences in methodology between the two studies render further conclusions difficult. Nevertheless, given the almost identical results between the two groups in this study, we believe that a trial with larger sample sizes may show that the pharmacokinetics of propofol in postpartum patients are closer to those in patients undergoing Caesarean section than those in non-pregnant patients.

We have postulated that pharmacokinetics in women undergoing Caesarean section may be influenced by both the physiological changes of pregnancy and the operative procedure. The findings in this study imply that the blood volume changes and loss of placental and fetal compartments at Caesarean section do not have a significant effect on the pharmacokinetics of propofol in women during the peripartum period. The increased clearance may be related to an increase in the extrahepatic metabolism of propofol by enzyme induction or increased blood flow to other organs where metabolism is suspected to occur. Another possibility is that the increased cardiac output in pregnancy may redistribute propofol back more quickly from peripheral tissues for metabolism as the terminal elimination of propofol is constrained normally by the slow return of propofol from peripheral compartments.

Maternal and fetal proteins have similar drug binding affinity and differences in concentrations of binding proteins or displacing substances are responsible for the fetal to maternal distribution of drugs at steady state [17]. Lower protein binding in the fetus is seen usually with basic drugs which bind to α_1-acid glycoprotein. However, the situation is more complex and uncertain with propofol, as it is a very weak acid which binds to red blood cells and to plasma proteins.

UV:MV and UA:UV ratios of propofol concentrations were similar to those reported and discussed in previous studies [2, 18]. The elimination of propofol in the neonate appears to be slower than that in the mother, but this is to be expected with most drugs, including thiopentone [19]. The V^{ss} for propofol in the neonate has not been determined, but V^{ss} is usually increased in neonates compared with adults [20]. It is likely that clearance of propofol may be decreased also, as neonatal glucuronidation is developed poorly, despite a sulphation activity which is similar to that found in adults [20]. Nevertheless, the neonatal concentrations of propofol were very small and neonatal assessment was satisfactory.

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GASTRIC EMPTYING IN PREGNANCY

A. G. MACFIE, A. D. MAGIDES, M. N. RICHMOND AND C. S. REILLY

SUMMARY

The rate of gastric emptying in pregnancy was measured indirectly using the rate of paracetamol absorption in four groups of 15 patients: non-pregnant controls, first trimester patients presenting for termination of pregnancy, second trimester patients presenting for prostaglandin termination of pregnancy, and patients presenting for elective Caesarean section. All patients were fasted for 6 h and then received paracetamol tablets 1.5 g orally with water 50 ml. Blood samples were taken at 15-min intervals for 120 min and analysed for paracetamol concentration. There was no significant difference between the groups in the maximum concentration and time to maximum concentration (ANOVA). The AUC was reduced for the first trimester group at 60 and 120 min ($P < 0.05$). No significant delay in gastric emptying was demonstrated in any of the three trimesters of pregnancy compared with the control group.

KEY WORDS

Gastrointestinal tract: gastric emptying. Pregnancy gastric emptying.

It has been postulated widely that there may be a delay in gastric emptying in pregnancy resulting from either hormonal or mechanical factors [1, 2]. Smooth muscle relaxation caused by progesterone would lead to inhibitory effects on gastric emptying commencing early in pregnancy and lasting throughout the pregnancy, whereas mechanical obstruction caused by a gravid uterus would assume importance in the last trimester of pregnancy. Delay in gastric emptying in pregnancy may contribute to the risk of regurgitation during anaesthesia [3] and also delay absorption of orally administered drugs, such as H_2-receptor antagonists.

However, evidence regarding delay in pregnancy is inconclusive at present. Studies with dye aspiration have produced conflicting results [4, 5]. Measurement of gastric emptying using x-ray follow-through [6] and epigastric impedance [7] have suggested there is no delay during pregnancy, but there may be during labour, whereas another barium follow-through study found a delay in only one patient in 12 in labour [8].

The paracetamol absorption technique has been used extensively as an indirect measure of gastric emptying. It has been used to measure gastric emptying in labour; delayed emptying occurred only in women who received opioids [9]. A more recent study [10], found a significant delay in the absorption of paracetamol, and therefore gastric emptying, in parturients of 12–14 weeks gestation compared with non-pregnant controls.

The aim of this study was to use the rate of absorption of paracetamol as an indirect measure of gastric emptying in patients in each of the three trimesters of pregnancy and a non-pregnant control group.

PATIENTS AND METHODS

Following local Ethics Committee approval and written informed consent, we studied 60 patients allocated to four groups: 15 non-pregnant women before minor gynaecological surgery (control), 15 women in the first trimester before suction termination of pregnancy (TOP), 15 women in the second trimester before prostaglandin extra-amniotic termination of pregnancy (PG) and 15 women in the third trimester before elective

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Caesarean section (CS). Gestation was determined by the gynaecologists on the basis of clinical examination and ultrasound scan where clinically indicated. All patients were healthy and were not taking any drugs likely to affect gastric emptying. All patients were fasted for a minimum of 6 h and were studied on the morning of surgery before administration of any premedication.

Gastric emptying was measured using the paracetamol absorption technique described by Heading and colleagues [11]. The patient remained in bed in a comfortable sitting position for the duration of the sampling. An 18-gauge i.v. cannula was inserted into a peripheral vein after local anaesthetic infiltration and a baseline sample of 8 ml of blood withdrawn at this time. Each patient ingested three paracetamol tablets (1.5 g) (Winthrop Laboratories) with water 50 ml. Blood samples were taken at 15-min intervals for 2 h. The plasma was separated and stored at −20 °C for subsequent measurement of plasma concentration of paracetamol by high pressure liquid chromatography [12]. The lower limit of detection for paracetamol in our laboratory is 0.3 $\mu g\ ml^{-1}$; the coefficient of variance for measurement during this study was 0.55%. The peak paracetamol concentrations (*C*max) and the time of peak concentration (*tC*max) were recorded, and the area under the time–concentration curve (AUC) was calculated using the trapezoidal rule.

TABLE I. *Patient characteristics (median (range) or mean (SD)).* $*P < 0.05$; $***P < 0.001$

Group	Gestation (weeks)	Age (yr)	Weight (kg)
Control	—	30 (22–42)	63.13 (11.67)
TOP	10–12	23 (16–35)	62.00 (9.97)
PG	15–18	21 (16–25)***	60.20 (8.33)
CS	37–40	27 (22–35)	72.70 (7.20)*

The data were analysed for normality using the coefficient of variance, followed by analysis using one-way analysis of variance, with Tukey's HSD test between groups where appropriate.

RESULTS

Data for age, weight and gestation are shown in table I. There was no significant difference in age between control, TOP or CS groups. The PG group was significantly younger, with a mean age of 21 yr compared with 30.7 yr for controls ($P < 0.001$). The mean weight of the CS group was heavier than the other groups, as might be expected in patients at term pregnancy ($P < 0.05$).

The time–concentration curves of the mean plasma paracetamol concentrations for all four groups were similar (fig. 1). *C*max ranged from 28.2 $\mu g\ ml^{-1}$ in the control group to 23.0 $\mu g\ ml^{-1}$ in the TOP group (ns) (table II). *tC*max was

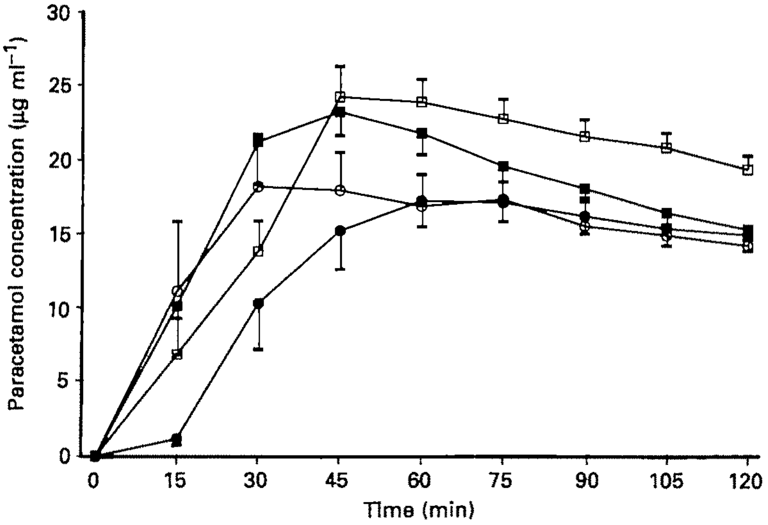

FIG. 1. Mean (SEM) plasma paracetamol concentrations after paracetamol 1.5 g orally, for time 0 to 120 min measured at 15-min intervals in patients in the control (□), TOP (●), PG (○) and CS (■) groups.

TABLE II. *Peak paracetamol concentrations (Cmax) and the time to peak concentration (tCmax) after paracetamol 1.5 g orally (mean (SEM))*

Group	Cmax (μg ml^{-1})	*t*Cmax (min)
Control	28.19 (1.62)	61 (6.85)
TOP	23.01 (2.18)	74 (8.54)
PG	26.70 (2.54)	59 (9.32)
CS	28.10 (2.12)	45 (4.89)

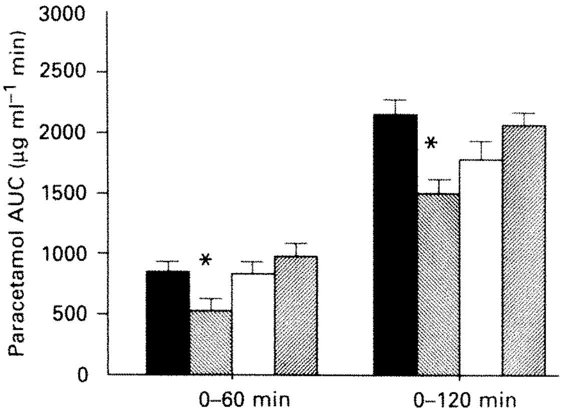

FIG. 2. Area under paracetamol time–concentration curve (AUC) for 0–60 min and 0–120 min for control (■), TOP (▧), PG (□) and CS (▨) groups. *$P < 0.05$.

61 min in the control group, fastest in the CS (45 min) and slowest in the TOP group (74 min) (ns) (table II).

The area under the paracetamol time–concentration curve (fig. 2) for 60 min (AUC_{60}) and for 120 min (AUC_{120}) was significantly smaller in the TOP group compared with the control group ($P < 0.05$). The power of the study was calculated to be greater than 80% ($P < 0.05$).

DISCUSSION

We have not demonstrated any significant delay in gastric emptying during the three trimesters of pregnancy, as measured by the rate of absorption of paracetamol. There was no significant difference with respect to the mean maximum concentration of paracetamol (*C*max) and the mean time to maximum concentration of paracetamol (*tC*max) for the four groups.

Part of the inconsistency in measurement of gastric emptying in pregnancy may be a result of the limited choice of method of measurement imposed by pregnancy. Invasive methods of measuring gastric emptying, such as radiology and scintigraphy, are ethically unacceptable in pregnancy. The use of the epigastric impedance technique depends on the administration of a large volume of liquid orally which is not desirable in the preoperative period. Therefore, the paracetamol absorption technique was used in this study as an indirect measure of gastric emptying. This method has been validated by comparison with the sequential scintiscanning radio-isotope technique [11] and the time taken for the half-time of gastric emptying has been shown to correlate with the peak maximum plasma concentration of paracetamol (*C*max) and the time to achieve that peak concentration (*tC*max). In this study, although there was a tendency towards a lesser *C*max and longer *tC*max in the first trimester TOP group, this was not statistically significant. The AUC for 60 and 120 min was significantly smaller in the TOP group, indicating that a lesser total amount of paracetamol was absorbed. This variable was not mentioned in the original method, and when described in a subsequent study [13] was accompanied by significant differences in *tC*max and *C*max. The difference in AUC in this study may reflect a combination of factors other than gastric emptying; for example, decreased small bowel transit time, or altered physiology in early pregnancy leading to altered hepatic or gastrointestinal blood flow. Volume of distribution may be increased in pregnancy, which might affect *tC*max and AUC.

No previous studies using the paracetamol absorption technique have examined gastric emptying in the three trimesters of pregnancy. A previous study [10] in early pregnancy did demonstrate a delay in gastric emptying using the paracetamol absorption technique in patients 12–14 weeks pregnant compared with pregnant patients of 8–11 weeks gestation and controls. However, the patients were studied supine, whereas the patients in this study were studied in the sitting position. The supine posture *per se* has been demonstrated to delay gastric emptying [14], and may exaggerate any physiological tendency to delay, although this does not explain the difference between the 8–11 week and 12–14 week groups. Many patients present for surgery at this gestation, and any delay in gastric emptying may have implications for anaesthesia. Therefore, further studies with larger numbers of patients or alternative methods of measuring gastric emptying might help to clarify this issue.

The CS group, although being the most likely to demonstrate any delay in gastric emptying because of mechanical factors, had the fastest *t*Cmax.

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CARDIAC FUNCTION IN ANEURYSMAL SUBARACHNOID HAEMORRHAGE: A STUDY OF ELECTROCARDIOGRAPHIC AND ECHOCARDIOGRAPHIC ABNORMALITIES

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SUMMARY

Electrocardiographic (ECG) changes are reported frequently after subarachnoid haemorrhage (SAH). The aim of this study was to investigate the functional significance of ECG changes by echocardiographic assessment of cardiac function. Forty-five patients with intracranial aneurysms were studied. All patients had a 12-lead ECG and a two-dimensional echocardiogram. After patients with an history of chronic cardiac disease (n = 4) were excluded, only four patients were found to have wall motion abnormalities. These patients had only minor ECG abnormalities, but severe neurological dysfunction. Conversely, patients with other ECG abnormalities including the deep inverted T waves associated usually with SAH, had normal echocardiograms. We conclude that the ECG is not an accurate predictor of myocardial function after SAH and that myocardial dysfunction is related more closely to severity of neurological condition.

KEY WORDS

Haemorrhage: subarachnoid. Heart: cardiac dysfunction. Monitoring: echocardiography, electrocardiography.

Electrocardiographic changes have been well documented after subarachnoid haemorrhage (SAH). In addition to T wave, S–T segment and Q–T interval abnormalities, changes in P wave and U wave configuration may be found, and arrhythmias [1–4]. Although these changes are not regarded usually as of great clinical significance because most of the patients do not have ischaemic heart disease and survive the perioperative period without overt adverse cardiac events, postmortem examinations frequently show focal myocardial haemorrhages and myocytolysis [5, 6]. In view of the latter, the electrocardiographic changes may have functional significance and may create a dilemma for the anaesthetist who sees the patient immediately before operation [7, 8]. The aim of this study was to assess the relationship between the electrocardiographic changes and an echocardiographic assessment of cardiac function.

PATIENTS AND METHODS

Forty-five patients with intracranial aneurysms, SAH, or both, were assessed. All patients had a 12-lead electrocardiogram and a two-dimensional echocardiographic study before operation. If more than a single electrocardiogram record existed, the one in closest temporal proximity to the echocardiographic study was used for assessment. Electrocardiograms were considered abnormal if the T wave was inverted or flattened, the S–T segment was elevated or depressed, the Q–T interval prolonged or a pathological Q wave or U wave was present. The presence of an arrhythmia or conduction defect was noted also. Bradycardia was defined as a heart rate less than 60 beat min^{-1} in patients not taking β-blockers. Axis deviation coincident with hypertension or pulmonary disease was not considered an acute change consistent with SAH.

The two-dimensional echocardiograms were recorded on a Panasonic Model Ag 6300 VHS

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recorder using a Hewlett-Packard phased-array ultrasound imaging system, model 77020A. Studies were performed with a 2.5-MHz transducer. Standard parasternal long axis, short axis, apical four chamber and two chamber views were obtained for analysis of left ventricular function [9]. The left ventricular short axis was recorded at the level of the base, mid ventricle and apical region. The basal region included both mitral valve leaflets and chordal structures, while the mid ventricular region was at the level of the papillary muscles and the apex was defined as the region extending from the most distal aspects of the papillary muscles to the ventricular apex. The videotape recordings were reviewed by an experienced echocardiographer (D.R.B.) without knowledge of the patient's neurological state. For purposes of analysis, the left ventricle was considered as divided into five segments consisting of the septum, anterolateral wall, posterolateral wall, posterior wall and apex. Wall motion in each segment was classified as normal, hypokinetic, akinetic or dyskinetic on the basis of a visual assessment of wall thickening and endocardial movement during systole. Normal myocardium showed inward movement of the endocardium with accompanying systolic wall thickening. Hypokinetic myocardium was defined as a reduction in wall thickening equal to or greater than 50% compared with normal segments. Akinetic segments had no systolic thickening and dyskinetic segments were defined as having paradoxical outward extension with systolic thinning [10]. The echocardiographic findings of mitral valve prolapse or ventricular hypertrophy were not considered as acute changes related to SAH.

Patient records were reviewed for age, sex, acute or chronic neurological deficits, acute or chronic cardiac disease and serum electrolytes. The Botterell classification of clinical status after SAH was used [11].

RESULTS

Forty-three patients had angiographic evidence of at least one intracranial aneurysm. Two patients had suffered SAH, but no aneurysm was found on angiography. Thirty-five patients (28 females, seven males; ages 18–71 yr) had SAH (neurological grade 1–4). The remaining 10 (seven females, three males; ages 40–69 yr) did not bleed from their aneurysm (neurological grade 0) (table I). The mean time between ictus and the electrocardiogram was 7.9 (SD 8.0) days (range 0–30 days). All echocardiograms were obtained after an electrocardiogram; mean time between the two tests was 2.8 (2.4) days.

Table I shows the distribution of patients according to the presence and absence of electrocardiographic and echocardiographic changes. Four patients (9%) with SAH had electrocardiographic or echocardiographic changes that were consistent with their history of chronic ischaemic cardiac disease, that is, Q waves on the electrocardiogram and an history of previous myocardial infarction. Table II shows the results with these patients excluded.

In the group with no history of cardiac disease (table II), 23 (56%) had no electrocardiographic or echocardiographic abnormalities. Eighteen patients (44%) had electrocardiographic changes, consisting of T wave inversion (four patients), T wave flattening (four patients), sinus tachycardia (four patients), sinus bradycardia (five patients), P

TABLE I. *Number of patients with abnormalities of the ECG and echocardiogram (ECHO) as defined in text. *Includes a patient who died*

	Neurological grade					
	0	1	2	3	4	Total
ECG normal ECHO normal	7	13	3			23
ECG acute change ECHO normal	3	9	2	2	2*	18
ECG acute change ECHO motion abnormality				3*	1*	4
Total	10	22	5	5	3	45

TABLE II. *Number of patients without heart disease with abnormalities of the ECG and echocardiogram (ECHO) as defined in the text. *Includes a patient who died*

	Neurological grade					
	0	1	2	3	4	Total
ECG normal ECHO normal	7	13	3			23
ECG acute change ECHO normal	1	8	2	1	2*	14
ECG acute change ECHO motion abnormality				3*	1*	4
Total	8	21	5	4	3	41

TABLE III. *ECG abnormalities in patients with abnormal echocardiogram (ECHO) (abnormalities as defined in text). *Indicates a patient who died*

Neurological grade	ECG	ECHO
3	Inverted T waves in I, AVL, V_{2-6}	Akinetic apex and anterolateral wall
3	Flattened T waves I, V_{5-6}	Hypokinetic apex
3*	Sinus tachycardia Flattened T waves I, V_{4-6}	Hypokinetic septum
4*	Sinus tachycardia Intraventricular conduction delay	Akinetic posterior lateral wall Hypokinetic apex

wave enlargement, ectopy and small inferior Q waves (one patient each) and conduction abnormality (two patients). Elimination of patients who had only rhythm or conduction abnormalities (seven patients) would remove one grade 4 patient with echocardiographic and electrocardiographic changes (table III), one grade 3, one grade 0, and four grade 1 patients from table II. Four of the 18 patients (22 %) with electrocardiographic abnormalities also had echocardiographic changes. The changes were either hypokinesis or akinesis and involved at least 30 % of the heart (table III). Two of the four patients with electrocardiographic and echocardiographic changes died within 7 days from complications of SAH (neurological grade 3 and 4). There was one death among the 14 patients with electrocardiographic abnormalities but without echocardiographic abnormalities (median Botterell class = 1.0). There were no deaths in the 23 in whom both electrocardiogram and echocardiogram were normal.

Both anterior and posterior circulation aneurysms were well represented in our study, yet bleeds associated with echocardiographic changes appeared confined to the anterior circulation (one carotid, three anterior communicating), whereas the majority with only electrocardiographic changes had posterior circulation aneurysms.

None of the electrocardiographic changes was associated with abnormal electrolyte concentrations.

All echocardiographic abnormalities occurred in patients with either severe SAH (Botterell grades 3 and 4; $P < 0.01$ compared with grade 0–2 patients) or an history of chronic ischaemic heart disease. No patient had echocardiographic abnormalities associated with an entirely normal electrocardiogram, but the abnormalities were minor in three (flattened T waves or intraventricular conduction delay, or both). However, none of the patients with the deep inverted T waves usually associated with SAH had echocardiographic abnormalities (table III).

Of 24 patients without a previous history of hypertension, 10 were found on admission to hospital to have sustained increases in arterial pressure. Two patients with both electrocardiographic and echocardiographic changes had severe hypertension (systolic > 200 mm Hg and diastolic > 100 mm Hg) while the other eight, only

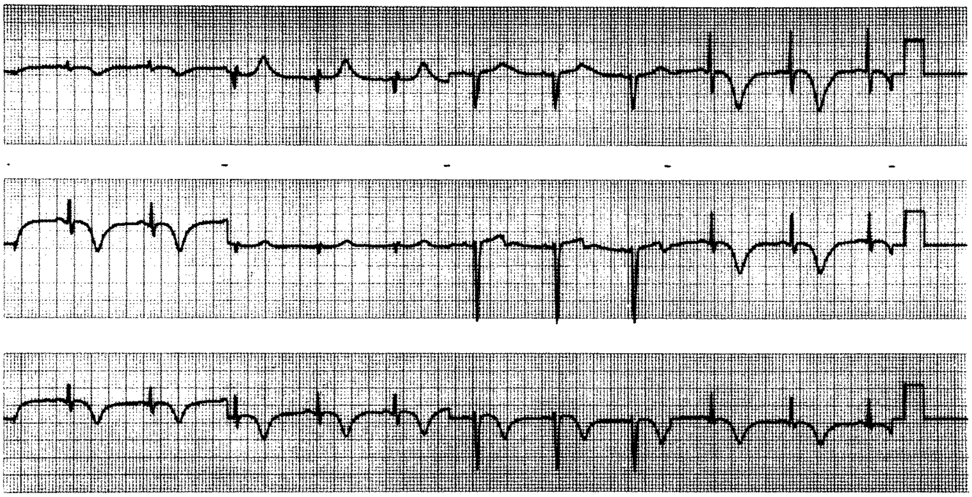

FIG. 1. Patient 1. The electrocardiogram shows normal sinus rhythm with prominent T wave inversion in leads 1, 2, 3, aVf, V_{3-6}. The associated echocardiogram was normal.

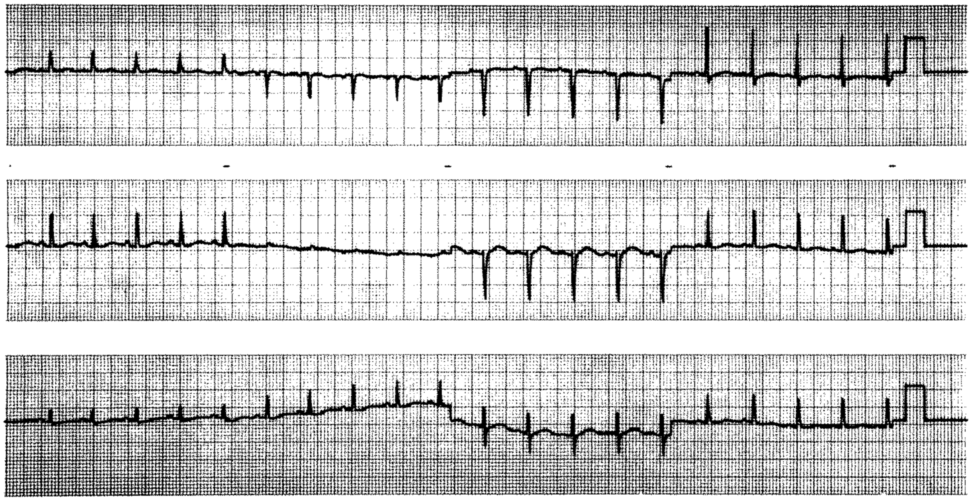

FIG. 2. Patient 2. The electrocardiogram shows sinus tachycardia with mild T wave flattening. The echocardiogram showed hypokinesis of the intraventricular septum.

three of whom had an electrocardiographic abnormality and none of whom had echocardiographic changes, had considerably smaller increases in arterial pressure.

Illustrative cases

Patient 1. A 31-yr-old woman in previously good health presented with an acute SAH from a ruptured posterior inferior cerebellar aneurysm. She was classified as grade 1. There was no acute cardiovascular instability or history of cardiac disease. Serum electrolyte concentrations were normal on admission. An electrocardiogram at that time showed normal sinus rhythm with very prominent T wave inversion in leads 1, 2, 3, aVf and $V_{3\text{-}6}$ (fig. 1). The following day a two-dimensional echocardiogram showed no abnormality. The patient was discharged 9 days later in good condition, following surgery.

Patient 2. A 43-yr-old woman in previously good health presented with an acute SAH from an anterior communicating aneurysm. Her neurological grade was 1. There was no acute cardiovascular instability or history of cardiac disease. Serum electrolyte concentrations were normal. Electrocardiogram obtained at the time showed sinus rhythm without abnormality. A two-dimensional echocardiogram was normal.

Ten days after admission, the same patient had another acute SAH. Her new neurological grade was 3. She had a sustained increase in systolic arterial pressure to more than 200 mm Hg. An electrocardiogram showed sinus tachycardia and minimal T wave flattening which was not present the previous week (fig. 2). A two-dimensional echocardiogram showed new localized hypokinesis of the intraventricular septum. The patient's neurological condition deteriorated over the next 3 days, at which time she died. Serum myocardial iso-enzyme concentrations did not support a diagnosis of myocardial infarction. Consent for an autopsy was not obtained.

DISCUSSION

Acute changes in the electrocardiogram are often indicative of cardiac disease which warrants a thorough but time consuming clinical investigation. However, the electrocardiographic changes after subarachnoid haemorrhage, which are usually regarded as not indicative of significant cardiac dysfunction, may cause urgent surgery to be delayed [7, 8]. By echocardiographic examination, we attempted to determine if these electrocardiographic changes represent cardiac dysfunction.

Appearing within the first 14 days after SAH, ECG changes may take up to 6 weeks to resolve [3]. Possible causes of these changes include abnormal electrolyte concentrations, vagal stimulation and hypothalamic dysfunction resulting in sympathetic stimulation [5, 12, 13]. Disturbances in serum electrolyte concentrations have been demonstrated after SAH and some of the electrocardiographic changes after SAH resemble those present in patients with such disturbances [12].

However, in our patients, we found no relationship between serum electrolyte concentrations (in particular potassium and calcium) and electrocardiographic changes. Other investigators also have found no relationship between serum potassium concentration and electrocardiographic aberrations [14, 15]. Only five patients had sinus bradycardia on electrocardiogram, but we cannot exclude vagal mechanisms at the time of the bleed.

Hypothalamic lesions after SAH have been associated with myocardial damage [16]. It is postulated that microinfarcts from cerebral artery spasm form in the hypothalamus after SAH [17]. As the hypothalamus is a centre for autonomic control, this leads to derangement of the sympathetic nervous system with increased catecholamine stimulation of the myocardium, both directly via the cardiac nerves and indirectly via the adrenal medulla [12]. Pathological examination of the heart after SAH may be grossly normal, but microscopic subendocardial haemorrhages and myocytolysis are often present [5, 6]. From experimental studies in which animals had the heart denervated, the adrenal glands removed or were treated with β-blockers or reserpine, it appeared that direct neural input to the heart was the most important [18, 19]. There is also an associated increase in release of corticosteroid after SAH which potentiates the effects of catecholamines [20].

Fifty-two percent of our patients with an intracranial bleed had electrocardiographic abnormalities that were unexplained by chronic disease. This is consistent with other reports in the literature [3, 13, 14]. Of interest in our study is the fact that those patients with the prominent large inverted T waves associated usually with SAH had normal echocardiographic studies (for example our patient 1). In contrast with some other studies, we found no relationship between the type of electrocardiographic changes and the level of consciousness, hypertension or mortality [2, 21]. The four patients with abnormal echocardiograms had minor electrocardiographic alterations.

Echocardiogram abnormalities appear to reflect the severity of subarachnoid bleeding. Patients with abnormal echocardiogram results averaged two Botterell grades worse, suggesting myocardial dysfunction is related to a worse neurological grade. In addition, their prognosis is poor, as two of the four succumbed to their disease. In contrast, all 28 of 29 patients with a normal echocardiographic study after SAH were discharged home from hospital. This is consistent with an earlier smaller study in which wall motion abnormalities corresponded with increased neurological grade and poorer outcome [22]. The sensitivity of the echocardiogram is greatly enhanced if the study is performed while the subject is stressed, for example during exercise. We did not feel that it would be ethical deliberately to stress patients with a SAH, and so may have missed some patients with myocardial dysfunction. Conversely, those with the worst neurological grade were probably the most stressed, and this may partly or completely explain their incidence of echocardiographic changes.

None of our patients died as a direct result of their cardiac dysfunction. This is consistent with other studies [23, 24]. Neurological status is the most important determinant of outcome and death is usually the direct result of the brain injury. Whereas cardiac dysfunction is not a direct cause of mortality after SAH, it may increase morbidity because of arrhythmias or pulmonary oedema [25].

Several methodological issues deserve comment. Some of our patients were not admitted until several days after SAH. There is the possibility that acute and quickly resolving changes in the electrocardiogram were missed in some subjects. Similarly, there was a delay between the electrocardiogram and the echocardiogram which may have resulted in us missing rapidly resolving echocardiographic changes. The definition of electrocardiographic abnormality we used was less precise than that used currently in relation to ischaemic heart disease, but is consistent with that used previously in relation to SAH [1–4]. Elimination of patients who had only rhythm or conduction abnormalities would not alter our conclusions. Although our sample size is substantially larger than the previous study of echocardiographic dysfunction in SAH [22], our sample is still too small to allow detailed statistical analysis. Confirmation of these results in a much larger study is desirable.

In conclusion, we found a poor relationship between electrocardiographic changes after SAH and evidence of myocardial dysfunction on the echocardiogram. A better relationship existed between the echocardiogram and the severity of the neurological injury. We suggest that, in the absence of a history of cardiac disease, the neurological grade be regarded as a risk factor for myocardial dysfunction, especially if it is associated with an abnormal electrocardiogram.

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NON-INVASIVE MEASUREMENT OF CARDIAC OUTPUT DURING INDUCTION OF ANAESTHESIA AND TRACHEAL INTUBATION: THIOPENTONE AND PROPOFOL COMPARED

A. VOHRA, A. N. THOMAS, N. J. N. HARPER AND B. J. POLLARD

SUMMARY

We have investigated the haemodynamic changes in response to induction of anaesthesia and tracheal intubation in patients who received either thiopentone 5 mg kg^{-1} or propofol 3 mg kg^{-1} followed by atracurium 0.5 mg kg^{-1} and fentanyl 1.5 μg kg^{-1}. Anaesthesia was maintained with 0.6% enflurane and 50% nitrous oxide in oxygen with assisted ventilation. Cardiac output and heart rate (HR) were monitored continuously with a transthoracic impedence monitor. Mean HR did not change after induction in each group, but increased after tracheal intubation in both groups ($P < 0.01$). Mean cardiac index (CI) decreased after induction ($P < 0.05$) and decreased further after tracheal intubation in both groups ($P < 0.05$). There was no difference between the two groups with respect to changes in CI and HR. Mean arterial pressure (MAP) and systemic vascular resistance (SVR) did not change significantly after induction in the thiopentone group. Both variables increased from preinduction values 1 min after tracheal intubation ($P < 0.001$). In contrast, both MAP and SVR decreased after induction in the propofol group ($P < 0.001$) and did not differ from preinduction values 1 min after tracheal intubation. MAP and SVR were greater in the thiopentone group compared with the propofol group after induction and tracheal intubation ($P < 0.01$).

KEY WORDS

Anaesthetics, intravenous. propofol, thiopentone Heart: cardiac output. Intubation, tracheal.

Since the first report by King and colleagues [1], the haemodynamic consequences of tracheal intubation have been investigated widely, and many methods of obtunding the pressor response have been evaluated. Because of difficulties in the measurement of cardiac output (CO), these studies have been confined mainly to the measurement of changes in heart rate (HR) and mean arterial pressure (MAP). The Bomed non-invasive continuous cardiac output monitor (BOMED) measures continuously changes in the thoracic electrical impedence to a 2.5-mA, 70-KHz alternating current during the cardiac cycle. These measured changes are used to derive a value for cardiac output using the Bernstein modification of the Sramek formula [2] and is updated continuously on a 12-heartbeat cycle. The measurements have been shown to correlate well with those derived using thermodilution techniques [3–9] and they follow CO trends as well as, if not better than, thermodilution techniques [4, 7, 10]. This study was designed to examine the effects of induction of anaesthesia and tracheal intubation in patients of ASA grade I or II receiving either propofol or thiopentone given as part of a balanced anaesthetic technique.

PATIENTS AND METHOD

After receiving local Ethics Committee approval, we obtained informed consent from 32 female patients of ASA grade I or II undergoing laparoscopy. Patients were premedicated with temazepam 20 mg given orally 1 h before operation. On arrival of the patient in the anaesthetic

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TABLE I. *Patient characteristics (mean (range or SEM)). Induction of anaesthesia was with propofol (group P) or thiopentone (group T). BSA = body surface area*

	Age (yr)	BSA (m^2)	Height (cm)	Weight (kg)
Group P	30.1 (25–39)	1.61 (0.04)	159 (1.8)	59.7 (2.6)
Group T	29.7 (19–44)	1.66 (0.03)	158 (1.6)	65.5 (3.2)

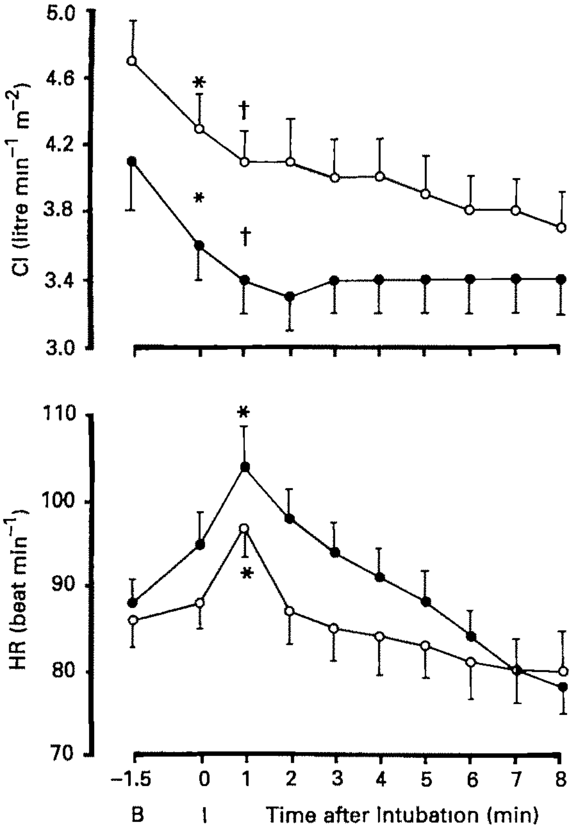

FIG. 1. Changes in cardiac index (CI) and heart rate (HR) after induction of anaesthesia and tracheal intubation (mean, SEM) in patients given thiopentone (●) or propofol (○). Significant changes ($P < 0.05$): * from baseline (B); † from preintubation value (I).

room, an 18-gauge cannula was inserted into a vein in the antecubital fossa. Non-invasive arterial pressure was measured using an automated method (Dinamap). Following skin preparation, two thoracic sensing electrodes (Medicotest-VL-00-S) were placed at the level of the xiphoid in each mid axillary line. Two cervical sensing electrodes were placed laterally at the root of the neck. Two current sensing electrodes were positioned 5 cm above the cervical and 5 cm below the thoracic sensing electrodes and connected to the BOMED (BoMed NCCOM3, software version 6, BoMed Biomedical, Irvine, CA). The waveform derived by the BOMED was monitored. A period of 5 min was allowed for the patient's recordings to stabilize. The preinduction (baseline) measurements of MAP, CO and HR were recorded.

Patients were allocated randomly to one of two equal groups to receive either thiopentone 5 mg kg^{-1} or propofol 3 mg kg^{-1} given over 20 s. The induction agent was followed immediately by fentanyl 1.5 µg kg^{-1} and atracurium 0.5 mg kg^{-1}. Tracheal intubation was performed 90 s after induction of anaesthesia by the same anaesthetist on every occasion. The view of the larynx during laryngoscopy was graded according to the classification described by Cormack and Lehane [11]. The patient was excluded from the trial if the vocal cords were not visualized (laryngoscopic grade 3 or 4). Anaesthesia was maintained subsequently with 0.6 % enflurane and 50 % nitrous oxide in oxygen. Ventilation was assisted using a Manley MP2 ventilator and normocapnia maintained and monitored with a capnograph. Further recordings of HR, MAP and CO were made 90 s after induction of anaesthesia (just before tracheal intubation) and at 1-min intervals for 8 min after tracheal intubation.

The patient's body surface area (BSA) was derived from a standard nomogram for height and weight [12]. Cardiac index (CI) and systemic vascular resistance (SVR) were calculated using the standard formulae. All data were analysed using paired and unpaired *t* tests as appropriate and multivariate analysis of variance (MANOVA).

RESULTS

There was no difference in height, weight, age or BSA between the patients given thiopentone (group T) or propofol (group P) (table I). One patient was excluded from the trial because of

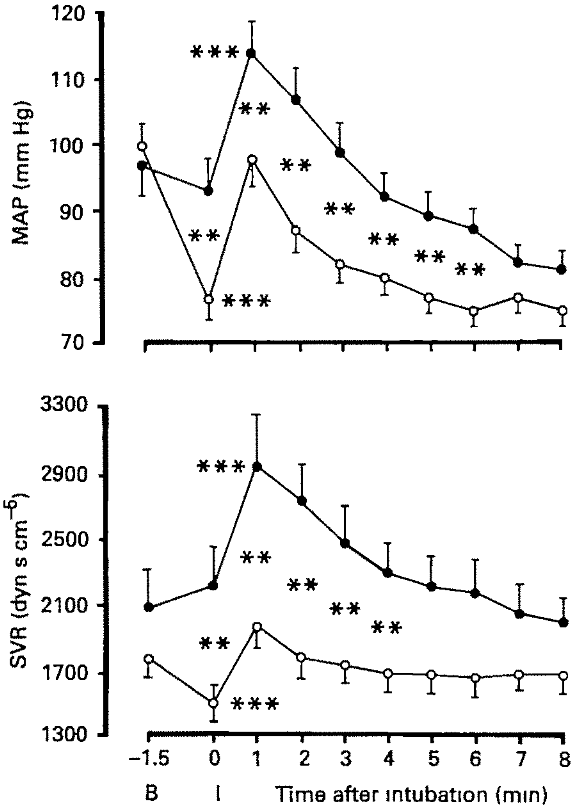

FIG. 2. Changes in mean arterial pressure (MAP) and systemic vascular resistance (SVR) following induction of anaesthesia and tracheal intubation (mean, SEM) in patients given thiopentone (●) or propofol (○). ** Significant difference between groups ($P < 0.01$); *** Significant change from baseline (B) ($P < 0.001$).

difficulty with tracheal intubation (laryngoscopic grade 3). There were thus 16 patients in group P and 15 in group T. None of the patients coughed at tracheal intubation.

Cardiac index

There was no difference in the mean baseline CI or in response to induction and tracheal intubation (fig. 1) in the two groups. Induction of anaesthesia was associated with a decrease in CI in both groups ($P < 0.05$) and a further decrease 1 min after tracheal intubation ($P < 0.05$).

Heart rate

There was no difference between the two groups in the mean baseline HR or in the response to induction and tracheal intubation (fig. 1). Induction of anaesthesia did not change HR in each group and there was a significant increase in HR in both groups 1 min after tracheal intubation ($P < 0.01$).

Mean arterial pressure

The mean baseline MAP was not significantly different between the two groups (fig. 2). Induction with propofol was associated with a significant decrease in MAP ($P < 0.001$) which did not occur in group T. MAP increased in both groups 1 min after tracheal intubation. The MAP was significantly greater in group T after induction (MANOVA $P < 0.01$). Individual t tests identified these differences to be before and 6 min after tracheal intubation ($P < 0.01$). The 1-min post-intubation MAP readings were compared with preintubation MAP. There was no difference between the two groups in the degree of change in MAP in response to tracheal intubation.

Systemic vascular resistance

Mean SVR (fig. 2) decreased after induction with propofol ($P < 0.001$), but not after thiopentone. SVR was greater in group T after induction compared with group P ($P < 0.01$). One minute after tracheal intubation, SVR increased from baseline in the thiopentone group ($P < 0.001$), whereas after propofol it returned to baseline. There was no difference between the two groups in the degree of change in SVR in response to tracheal intubation.

DISCUSSION

In this study cardiac index decreased after induction of anaesthesia in both groups. However, we found that there was no difference between the effects of thiopentone and propofol on CI. The changes in HR and MAP are comparable to those observed in other studies. The vasodilator effect of propofol [13] was confirmed by the greater reduction in SVR after induction of anaesthesia in group P compared with group T. The changes in MAP were a reflection of these changes in SVR in both groups. This may explain why, in comparison with baseline values, hypertension occurs in response to tracheal intubation after induction of anaesthesia with thiopentone but not after propofol [14].

The bioimpedence method (Q_{BI}) offers a simple, non-invasive method for measurement of CI in ASA I or II patients. It has been compared extensively with the thermodilution method (Q_{TD})

mainly, but not exclusively [7, 9, 10], in the critical care setting. The reported correlation coefficients vary between 0.62 and 0.97 [3–10]. When assessing reliability, the coefficient of variation has been found to vary between 5.1% and 8.9% with Q_{BI}, compared with 8.1–18.6% with Q_{TD} [7, 8, 10]. It has been calculated that a 5–10% change in CO may be detected reliably with 25–100 measurements [15]. The work by Sullivan and colleagues [9] is more relevant to this study because they compared Q_{BI} with Q_{TD} in patients undergoing anaesthesia for aortic aneurysm surgery. The measurements were made awake, following induction, following tracheal intubation, before skin incision and at stages during the surgical procedure. All these studies show that Q_{BI} consistently neither underestimates nor overestimates CO in comparison with Q_{TD} and that it is reliable.

The similarity in haemodynamic changes in response to tracheal intubation in the two groups may suggest that there is no difference between the two agents, thiopentone and propofol, in their effects on the mechanisms underlying the pressor response to tracheal intubation. The dose equivalence ratio of thiopentone:propofol (1:1.6) is based on work by Grounds, Moore and Morgan [16]. They studied unpremedicated patients and did not administer any other anaesthetic agent. The doses we used are extrapolated from those used in their study. We cannot assume, therefore, that the ratio ensures equipotency and some may consider the dose of propofol to be large. In addition, enflurane and IPPV may have affected our findings and the small dose of fentanyl given at induction is known to obtund [17], although not abolish, the pressor response to tracheal intubation.

The continued decrease in CI after tracheal intubation (when concomitant increases in HR and MAP occurred) was an unexpected finding. We might have expected to see an increase in CI in response to tracheal intubation because of release of catecholamines at this time [18–20]. Although Moffit and colleagues [21] found such an increase in CI after tracheal intubation, Patrick and coworkers [22] found a lower CI after tracheal intubation in patients undergoing coronary artery surgery. Barash, Kopriva and Giles [23], using a radionuclide technique, found a decrease in stroke volume in response to tracheal intubation in patients without cardiovascular disease. Possible explanations for this unexpected decrease in CI include the effects of IPPV [24] in addition to those of thiopentone, propofol and enflurane on myocardial contractility. A small preload or a large afterload may also lead to a decrease in CO. These changes might result from the effects of the instantaneous release of catecholamines on the pulmonary and systemic circulations. The balance between the positive and negative inotropic effects at the time of tracheal intubation is clearly important, and the decrease in CI may be simply a result of a persisting negative inotropic effect of the anaesthetic agents which is greater than any positive inotropic effect of the catecholamines released in response to tracheal intubation. This requires further investigation.

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EFFECT OF THIOPENTONE, ETOMIDATE AND PROPOFOL ON SYSTEMIC VASCULAR RESISTANCE DURING CARDIOPULMONARY BYPASS

F. BOER, J. G. BOVILL, P. ROS AND H. VAN OMMEN

SUMMARY

We have studied the effect of thiopentone, etomidate and propofol on systemic vascular resistance (SVR) during cardiopulmonary bypass with constant pump flow in 30 patients undergoing elective coronary artery bypass surgery. SVR decreased to 78% of control values after thiopentone 4 mg kg^{-1}, to 72% of control after etomidate 0.3 mg kg^{-1}, and to 68% of control after propofol 2 mg kg^{-1}; it returned to control values 10 min after administration of thiopentone and propofol and 7 min after administration of etomidate. Analysis of variance showed that there were no significant differences in the changes in SVR between the groups.

KEY WORDS

Anaesthetic, intravenous · propofol, thiopentone, etomidate
Heart, vascular pressures

Most of the i.v. anaesthetic drugs cause, to a lesser or greater degree, cardiovascular depression. The observed cardiovascular effects of a drug are the result of complex interactions between changes in systemic vascular resistance (SVR), heart rate, baroreflex activity and myocardial contractility. Cardiopulmonary bypass (CPB) has been used to study the isolated effects of drugs on the peripheral circulation [1–3]. In a previous study we used this model to study the effect of propofol on SVR [4]. In the present study we have compared the effect of propofol, thiopentone and etomidate, in doses used for induction of anaesthesia, on SVR during CPB.

PATIENTS AND METHODS

We studied 30 patients undergoing elective aortocoronary bypass grafting (CABG) surgery. The study was approved by the local Ethics Committee and all patients gave informed consent. All patients were receiving β-adrenoceptor antagonists, calcium antagonists and nitrates which were continued until surgery. Lorazepam 2–4 mg sublingually was given 90 min before the patient arrived in the operating theatre, where an i.v. infusion was commenced and a radial artery catheter inserted under local anaesthesia. The radial artery catheter was connected to a disposable pressure transducer (Gobuplast, Hillegom, The Netherlands) which was calibrated electronically before surgery.

Anaesthesia was induced with sufentanil 4–8 μg kg^{-1}. Pancuronium 100 μg kg^{-1} was given to provide neuromuscular block and, after intubation of the trachea, the patient's lungs were ventilated with an oxygen–air mixture ($F\text{I}_{\text{O}_2}$ 0.5). Anaesthesia was maintained with sufentanil 0.05–0.1 μg kg^{-1} min^{-1}. During CPB the infusion of sufentanil was reduced to 0.025 μg kg^{-1} min^{-1}. CPB was conducted with a membrane oxygenator using non-pulsatile flow with a pump flow index of 1.6–1.8 litre min^{-1} m^{-2} and moderate hypothermia (26–28 °C). The extracorporal bypass circuit was primed with Ringer's solution 1400 ml, human albumin 200 ml and 20% mannitol 100 ml.

Any patient who had been given a vasoactive drug before or during CPB was excluded from the study. When nasopharyngeal temperature and pump flow had been stable for 5 min, patients were allocated randomly (coded envelope) to receive thiopentone 4 mg kg^{-1}, etomidate 0.3 mg kg^{-1} or propofol 2 mg kg^{-1}. Perfusion pressure, pump flow and temperature were measured every 30 s for a further 5 min. The mean value of SVR

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TABLE I. *Patient characteristics and pre-drug conditions for the three groups (mean (range or* SD)). *BSA = Body surface area*

	Thiopentone	Etomidate	Propofol
n	10	10	10
Age (yr)	59.8 (48–72)	66.0 (46–82)	60.8 (31–75)
Weight (kg)	74.6 (7.9)	80.5 (7.3)	80.0 (10.4)
BSA (m^2)	1.85 (0.13)	1.94 (0.14)	2.00 (0.14)
Perfusion pressure (mm Hg)	65.7 (11.5)	66.2 (9.3)	64.0 (4.8)
Flow (litre min^{-1})	3.48 (0.62)	3.67 (0.60)	3.80 (0.68)
Pa_{O_2} (kPa)	20.0 (6.4)	19.9 (9.7)	20.9 (3.8)
PCV	0.23 (0.04)	0.27 (0.04)	0.26 (0.03)

calculated during the last 2.5 min was taken as the control value. The test drug was injected into the venous inflow of the oxygenator and recordings continued for at least 10 min or until cardioplegic solution was given, the pump flow was changed or the aortic clamp was released.

In all patients, systemic arterial pressure measured via the radial artery was taken to indicate perfusion pressure during cardiopulmonary bypass. SVR was calculated as:

$$\text{SVR} = \frac{\text{perfusion pressure (mm Hg)}}{\text{pump flow (litre min}^{-1})} \times 80 \text{ dyn s cm}^{-5}$$

Patient data were compared by one-factor analysis of variance. SVR values were compared using three-factor block design analysis of variance, with group, individual and time as the factors (NCSS program, Hinze JL, Kaysville, Utah, U.S.A.). Differences within groups were compared using Fisher's LSD test. $P < 0.05$ was taken as statistically significant. Results are presented as mean (SD).

RESULTS

There were no statistically significant differences in patient data, pre-drug pump flow, perfusion pressure, Pa_{O_2} or PCV between the three groups of patients (table I). Complete recordings were obtained for 10 min for all patients in the propofol group and for eight patients in the thiopentone and etomidate groups.

SVR was significantly decreased compared with control by 1 min after drug administration in the etomidate and propofol groups and by 1.5 min in the thiopentone group (table II). It remained significantly less than control for 10 min in the thiopentone and propofol groups, and for 6 min in the etomidate group. Analysis of variance demonstrated no statistical difference between groups with respect to the time course of changes in SVR ($F = 0.75$, df = 266 and 18, $P = 0.7574$).

DISCUSSION

We have shown that thiopentone, etomidate and propofol, given during CPB in doses comparable to those used for induction of anaesthesia, caused similar and significant decreases in SVR. These findings are similar to those reported previously for propofol [4] and for thiopentone [5]. In contrast, Pauca and Roy [6] found that thiopentone 250 mg given during CPB resulted in only a temporary decrease in perfusion pressure, lasting 40 s. These investigators used a faster pump flow (2.0–2.8 litre min^{-1} m^{-2}) than we did, and this may have contributed to the shortlived hypotensive effect of thiopentone in their study.

The haemodynamic effects of propofol and etomidate have been studied in patients who had a Jarvik-7 artificial heart implant whilst waiting for cardiac transplantation [7]. The artificial heart was set to provide a constant cardiac output independent of changes in preload. This system is similar to our CPB model in that it allows the systemic vascular effects of a drug to be studied independent of changes in cardiac output or heart rate. In these patients, propofol 2.5 mg kg^{-1} reduced mean arterial pressure, and therefore SVR, by 61 % [7]. Arterial pressure remained significantly less than the pre-drug value for 30 min. In contrast to propofol, etomidate 0.3 mg kg^{-1} did not change any haemodynamic variables [8]. This is in contrast with our study in which etomidate caused a decrease in SVR similar to that produced by propofol. A possible ex-

TABLE II. *Changes in systemic vascular resistance (SVR) after thiopentone, etomidate or propofol (mean (SD)).* *$P < 0.05$. N = *No. patients*

	Thiopentone 4 mg kg^{-1}		Etomidate 0.3 mg kg^{-1}		Propofol 2 mg kg^{-1}	
Time (min)	*n*	SVR (dyn s cm^{-5})	*n*	SVR (dyn s cm^{-5})	*n*	SVR (dyn s cm^{-5})
Control	10	1768 (315)	10	1639 (183)	10	1528 (199)
0.5	10	1829 (357)	10	1733 (217)	10	1574 (205)
1	10	1790 (352)	10	1327 (256)*	10	1260 (323)*
1.5	10	1405 (310)*	10	1176 (282)*	10	1042 (271)*
2	10	1382 (393)*	10	1239 (289)*	10	1063 (246)*
2.5	10	1489 (446)*	10	1278 (246)*	10	1120 (260)*
3	10	1558 (459)*	10	1330 (258)*	10	1153 (260)*
3.5	10	1593 (489)*	10	1381 (292)*	10	1184 (246)*
4	10	1608 (480)*	10	1387 (248)*	10	1196 (243)*
4.5	10	1520 (389)*	8	1410 (264)*	10	1217 (247)*
5	10	1529 (396)*	8	1429 (257)*	10	1229 (244)*
6	9	1603 (362)*	8	1445 (265)*	10	1235 (250)*
7	8	1628 (368)*	8	1495 (280)	10	1253 (274)*
8	8	1640 (381)*	8	1537 (284)	10	1247 (265)*
9	8	1612 (311)*	8	1556 (279)	10	1243 (277)*
10	8	1647 (378)*	8	1554 (273)	10	1282 (237)*

planation for the decrease in SVR after etomidate and the other drugs in our patients could be an increase in the depth of anaesthesia from a previously inadequate level. We feel this is unlikely. No patient showed evidence of inadequate anaesthesia before the start of CPB. Although in this study we did not measure plasma catecholamine concentrations, in a previous study [4] in which an identical anaesthetic technique was used, plasma concentrations of adrenaline and noradrenaline were not increased 5–10 min after the start of cardiopulmonary bypass and did not change after administration of propofol. This suggests that anaesthesia with the doses of sufentanil used was adequate. A single bolus of sufentanil 1.3 µg kg^{-1} produced unconsciousness and a depth of anaesthesia adequate for laryngoscopy [9]. This dose is considerably less than that used in the present study.

Williams and colleagues [10] compared the cardiovascular effects of thiopentone 4 mg kg^{-1}, etomidate 0.3 mg kg^{-1} and propofol 2.5 mg kg^{-1} for induction of anaesthesia in patients with coronary artery disease. There were no significant changes in SVR after any of these drugs. Etomidate did not alter SVR in elderly patients undergoing upper abdominal surgery, whereas propofol resulted in a significant decrease [11]. The reported effects of propofol on SVR are conflicting. Whereas a decrease has been described [12], others found no decrease [13–15]. These differences may reflect differences in patient populations, combinations with other drugs and possibly the ventilatory status of the patient.

The differences in the systemic vascular effects of thiopentone, etomidate and propofol in our study and in those in which they were used to induce anaesthesia may be related to the circumstances pertaining during CPB. In particular, the use of non-pulsatile flow and hypothermia may have altered the sensitivity of vascular smooth muscle to the vasodilating effects of these drugs. The decrease in SVR produced by droperidol is of longer duration during non-pulsatile flow compared with pulsatile flow [3]. All three drugs are moderately to highly bound to plasma proteins: thiopentone 80–84% [16, 17], etomidate 70–75% [18, 19], propofol 98% [20]. Thus haemodilution during CPB results in an increase in the free fraction of unbound drug, with a corresponding increase in pharmacological effect. The free fraction of propofol increases 1.5–3 fold during bypass [21]. The use of heparin during CPB, by increasing non-esterified fatty acids, may further decrease the binding of drug to plasma proteins [22]. All our patients were taking β-adrenoceptor antagonists and calcium entry blockers. These drugs may have influenced the results. It is also possible that the large concentrations of sufentanil used during the study have altered systemic vascular sensitivity to the drugs studied. Sufentanil 6 $\mu g\,kg^{-1}$ causes significant vasodilatation in the isolated denervated hindlimb of the dog, an effect that is independent of opioid receptors [23]. Similar vasodilatation is produced by equivalent doses of fentanyl and alfentanil.

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EFFECT OF P6 ACUPRESSURE ON POSTOPERATIVE VOMITING IN CHILDREN UNDERGOING OUTPATIENT STRABISMUS CORRECTION

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SUMMARY

A prospective, double-blind study was conducted to compare the effect of pressure at the P6 (Neikuan) point with placebo as an antiemetic in children. Sixty-six patients, ages 3–12 yr, undergoing outpatient surgery for correction of strabismus, were allocated randomly to receive either bilateral P6 acupressure or placebo during the perioperative period. The study was designed to detect a 50% difference in the incidence of postoperative vomiting between the two groups, with a 90% power of achieving a statistically significant result at the 5% level (two-tailed). The incidence of postoperative vomiting for the placebo group was 58% before discharge from hospital, 73% at home and 82% in the first 24 h after surgery. The corresponding results for the acupressure group were 58% before discharge, 71% at home and 94% in the first 24 h. These differences were not significant; P6 acupressure did not reduce the incidence of postoperative vomiting in children undergoing strabismus surgery.

KEY WORDS

Acupuncture· acupressure, ophthalmological. Anaesthesia: paediatric Complications. nausea, vomiting.

Traditional Chinese medical practice includes the use of acupuncture in the management of a wide range of medical conditions. The first comprehensive textbook on the subject appeared around 200 B.C. [1]. Acupuncture and massage (t'ui-na) are techniques suitable for adult and paediatric practice [2–3]. Stimulation of the P6 (Neikuan or neiguan) wrist point is used for the treatment of nausea and vomiting [2]. Since 1986 there have been several studies in the English language medical literature reporting beneficial antiemetic effects from P6 stimulation in adults using either needling (acupuncture) or pressure (acupressure) [4–11]. The majority of these studies have investigated postoperative nausea and vomiting, but P6 stimulation has also been shown to be an effective antiemetic for symptoms associated with pregnancy [8] and chemotherapy [9, 10]. There have been no reports of P6 stimulation in the paediatric population.

Strabismus surgery in children is associated frequently with postoperative vomiting; without antiemetic therapy the incidence ranges from 52 to 85% [12–15]. Antiemetic drugs given during the perioperative period may be associated with unwanted side effects, including sedation, hypotension and extrapyramidal reactions [16, 17]. As there are no reported adverse reactions to P6 stimulation in the literature [7], we decided to study the efficacy of P6 stimulation as a postoperative antiemetic in children undergoing strabismus surgery. We felt that P6 acupressure, rather than acupuncture, would be more appropriate in children.

PATIENTS AND METHODS

Approval for the study was granted by the local Ethics Committee on Human Research, and informed consent obtained from the parents of all children before participation. We studied 66 children (ASA physical status I or II, ages

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3–12 yr) undergoing outpatient correction of strabismus. Children with anatomical or neurological abnormalities of the upper limbs were excluded from the study.

The P6 antiemetic point is the sixth point on the pericardial meridian; it lies at the wrist between the tendons of palmaris longus and flexor carpii radialis, 2 Chinese body-inches (ts'un) from the distal palmar crease [2]. In our study, bilateral acupressure was applied using "Sea-bands"—elasticated wrist bands available commercially for the prevention of seasickness: a plastic stud on the inner aspect of the band exerts continuous pressure at P6. Children participating in the study were allocated randomly to either an acupressure or a placebo group. The acupressure group wore Sea-bands and the placebo group wore bands without studs. Both types of band appeared identical unless turned inside out. The bands were positioned 1 h before operation by one investigator, and were worn continuously until discharge from hospital the same day. No one else involved in the study was aware of the type of band worn by an individual patient. Anxious or unco-operative children allowed the initial positioning of bands to be performed by their parents.

All children were allowed solids up to 8 h before operation and clear liquids (up to approximately 4 ml kg^{-1}) 3 h before operation. The children were unpremedicated, and the anaesthetic technique for both groups was identical. Induction of anaesthesia was with 1–5 % halothane and 66 % nitrous oxide and oxygen, administered via a face mask and Mapleson D system. The same agents, including 0.5–1 % halothane, were used for maintenance of anaesthesia. Following induction, the trachea was intubated using vecuronium 0.1 mg kg^{-1} i.v. to provide neuromuscular block and the lungs ventilated mechanically to an end-tidal carbon dioxide partial pressure of 4.0–4.7 kPa. During surgery, all patients received morphine 0.1 mg kg^{-1} i.v. for postoperative analgesia and atropine 0.01 mg kg^{-1} i.v. before manipulation of the eye, to prevent reflex bradycardia. At the end of surgery, the stomach was emptied with a suction catheter. Residual neuromuscular block was antagonized with atropine 0.02 mg kg^{-1} and edrophonium 1.0 mg kg^{-1}. All children received lactated Ringer's solution i.v. during the perioperative period. The hourly fluid requirements were calculated from the child's body weight as follows: 4 ml kg^{-1} for children up to 10 kg; an additional 2 ml kg^{-1} for each kilogram above 10 kg, up to 20 kg; and an additional 1 ml kg^{-1} for each kilogram above 20 kg. The total volume given was calculated to provide fluids for a 12-h period.

Standard monitoring was used throughout anaesthesia. Following tracheal extubation, the children were transported to the recovery area. After recovery (based on assessment of airway patency, vital signs and level of consciousness), they were transferred to the outpatient area. Children were discharged from hospital when, in addition to the previous criteria, they were able to ambulate and remained pain free. The ability to tolerate oral fluids was not included in the discharge criteria. Children were given droperidol 0.02 mg kg^{-1} i.v. for vomiting in hospital, at the discretion of the (blinded) anaesthetic staff. Prochlorperazine suppositories 5 mg were administered for treatment of vomiting at home, at the discretion of the parents. Paracetamol suppositories 10 mg kg^{-1} 4-hourly were prescribed for postoperative analgesia. Children did not wear eye patches following surgery. Patient characteristics were recorded by the first investigator when the bands were positioned. A second (blinded) investigator recorded all other perioperative data, including the incidence of postoperative nausea and vomiting in the recovery areas. Retching, defined as active efforts without expulsion of gastric contents, was graded as vomiting. Data after discharge from hospital were obtained by telephone interview within 48 h of surgery.

The sample size of our study was determined by power analysis [18]. Data from previous studies indicated that approximately 66 % of the placebo group would vomit after operation [13–16]. We considered that an antiemetic able to reduce the incidence of postoperative vomiting to 33 % would be clinically relevant. Thirty-one patients per group were therefore required to detect a 50 % difference in the incidence of vomiting between two groups, with a 90 % power (probability of a type II error = 0.1) of achieving a statistically significant result at the 5 % level (two-tailed). The presentation of data for continuous variables is given as the mean (SD), and were analysed using the unpaired Student's *t* test. Discrete variables were analysed using the chi-square test with Yates' continuity correction. $P < 0.05$ was considered statistically significant.

TABLE I. *Patient characteristics (mean (range or* SD*)). No significant differences between the two groups (unpaired* t *test or chi-square)*

	Placebo ($n = 33$)	Acupressure ($n = 31$)
Age (yr)	5.2 (3–12)	5.8 (3–12)
Weight (kg)	20.9 (8.0)	22.1 (9.2)
Sex (No. (%))		
Male	19 (58)	22 (67)
Female	14 (42)	11 (33)

TABLE III. *Incidence of postoperative vomiting (No. (%)) during the first 24 h after surgery for the two groups of children. No significant differences between the two groups (chi-square)*

	Placebo ($n = 33$)	Acupressure ($n = 31$)	P
Within hospital: 0–2 h	19 (58)	18 (58)	0.84
At home: 2–24 h	24 (73)	22 (71)	0.90
Overall: 0–24 h	27 (82)	29 (94)	0.30

RESULTS

Sixty-six children were entered to the study but, results from two children in the acupressure group were incomplete and they were excluded. There were no significant differences between the two groups in their patient characteristics (table I). The mean duration of anaesthesia and surgery, and the amount of i.v. fluid given in the perioperative period were the same in both groups. The total recovery time, taken from the end of anaesthesia to discharge from hospital, was 85–250 min (overall mean for both groups, 116 min). There was no significant difference between the mean total recovery times for each group. The wrist bands were worn for an average of 237 min, the bands were tolerated well and none had to be removed (table II). The number of eye muscles operated upon ranged from one to four (mode of two) in each group.

There was no significant difference in the incidence of vomiting between the two groups (table III); only eight children (six placebo, two acupressure) of 64 in the study did not vomit in the first 24 h after surgery. The frequency distribution for the number of episodes of vomiting per child in hospital was similar for both groups (fig. 1); no child had more than five episodes of vomiting. Droperidol was administered during recovery to 10 children (six placebo, four acupressure); eight of the 10 vomited at home (five placebo, three acupressure). Only one child in the study (placebo group) complained of nausea without vomiting whilst in hospital; that child vomited later at home. Five children (three placebo, two acupressure) had not taken oral fluids 24 h after surgery. There were no complications in each group, other than vomiting, following discharge. No child remained in hospital, and none required readmission within the period of follow-up.

DISCUSSION

We were unable to demonstrate a reduction in the incidence of postoperative vomiting in children undergoing strabismus surgery using P6 acupressure. This result should be considered in relation to previous studies investigating both vomiting in children following strabismus surgery, and the antiemetic effect of P6 stimulation in adults.

Several factors may have contributed to the high incidence of postoperative vomiting found in this study. These include surgical manipulation of the eye, opioid analgesia and ambulation. Strabismus surgery in children is associated with a high incidence of postoperative vomiting: values of 52% [12], 56% [13], 68% [14] and 85% [15] have been reported. Stretching of the eye muscles and visual sensory disturbance may be important

TABLE II. *Perioperative data (mean (*SD*)). No significant differences between the two groups (unpaired* t *test)*

	Placebo ($n = 33$)	Acupressure ($n = 31$)
Duration of surgery (min)	60 (36)	57 (28)
Duration of anaesthesia (min)	96 (33)	97 (29)
Total recovery time (min)	117 (30)	115 (32)
Total time spent wearing bands (min)	244 (64)	230 (46)
Total i.v. fluids (ml)	724 (174)	729 (148)

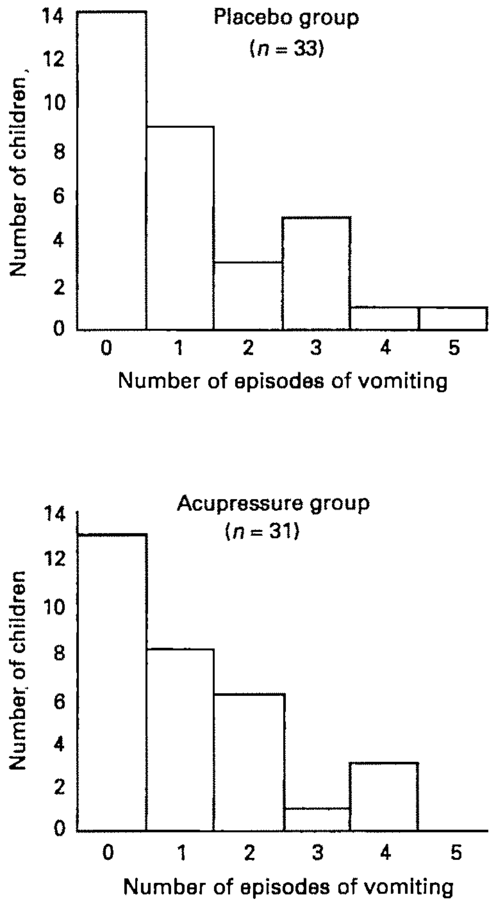

FIG. 1. Frequency distribution for the number of episodes of vomiting per child, before discharge from hospital.

factors in the aetiology of vomiting [12]. Droperidol 0.075 mg kg^{-1}, given before manipulation of the eye [14], is an effective antiemetic in this group of children. Smaller doses (0.05 mg kg^{-1}) appear to be ineffective [13, 15] and larger doses (0.1 mg kg^{-1}) may be associated with extrapyramidal reactions [16]. Postoperative pain in children caused by the operative procedure is common, and may delay recovery from the outpatient unit [17]. Unfortunately, the use of opioid analgesics in paediatric outpatient surgery is associated with a high incidence of vomiting after operation [19]. One study has investigated the effect of opioid analgesics on the incidence of vomiting in children after strabismus surgery: Lerman, Eustis and Smith [14] found that 68 % of children using i.m. codeine 1.5 mg kg^{-1} vomited, compared with 60 % using rectal paracetamol 10 mg kg^{-1}. This difference was not statistically significant. In the present study, we administered a small dose of morphine (0.1 mg kg^{-1} i.v.) during surgery, for postoperative analgesia.

Early ambulation may have increased the incidence of vomiting in our study, as the average time from the end of anaesthesia to discharge from hospital was 116 min (table II), compared with times of 3.3 h [13], 3.6 h [12] and 6.7 h [14] in three similar studies.

In 1986 Dundee and colleagues [4] reported the results of two consecutive studies using P6 acupuncture as a postoperative antiemetic. The patients were women, premedicated with either meptazinol or nalbuphine, undergoing minor gynaecological surgery of less than 12 min duration. Anaesthesia was induced and maintained with methohexitone, nitrous oxide and oxygen; no volatile agent was used. In patients premedicated with nalbuphine there was a significant reduction in the incidence of postoperative nausea and vomiting following preoperative P6 acupuncture needling, compared with either "dummy" acupuncture (administered at a site remote from P6) or no treatment. In patients premedicated with meptazinol, acupuncture was significantly better than no treatment alone; there was no dummy group in this study. Since this report, there have been several prospective studies of the antiemetic effect of P6 stimulation (both acupuncture and acupressure) reported in the English language medical literature. The majority of these studies have been reported by Dundee's group [4–10]. These authors demonstrated consistently that acupuncture is an effective postoperative antiemetic in women undergoing minor gynaecological surgery and premedicated with opioid analgesics (nalbuphine, meptazinol or pethidine) [4–7]. Dundee and colleagues [9] and Fitzpatrick, Ghaly and Dundee [10] also demonstrated that acupuncture was effective in reducing emetic symptoms in patients undergoing chemotherapy for testicular or breast cancer.

We decided that non-invasive P6 acupressure would be more acceptable than acupuncture in children. There are only three previous reports of the antiemetic effect of P6 acupressure in adults; all demonstrate beneficial results [7, 8, 11]. Dundee and colleagues [8] reported a significant ($P < 0.001$) decrease in emetic symptoms in a group of pregnant women treated with P6 acupressure, compared with two other groups, receiving either dummy acupressure (at a point remote to P6) or no treatment (controls). There was also a significant ($P < 0.01$) decrease in emetic symptoms in the dummy acupressure group, compared with controls. The authors stated that they were unable to exclude a psychological explanation for their findings. Fry [11] reported the incidence of postoperative nausea or vomiting in two groups of inpatients undergoing various surgical procedures, including ophthalmic surgery (16% of all procedures). Assessment was confined to the recovery period, and there was no information on premedication, anaesthetic technique or drugs given perioperatively. Forty of 250 controls complained of nausea, or vomited, compared with 11 of 250 in the group treated with digital P6 acupressure. This difference was significant ($P < 0.001$). Dundee and colleagues [7] pooled their data on postoperative vomiting from more than 500 women, all premedicated with nalbuphine, undergoing minor gynaecological surgery. There were four groups of patients; each received a different type of P6 stimulation: manual acupuncture needling, electrical stimulation of acupuncture needles, non-invasive electrical stimulation, or acupressure using Sea-bands. All four groups showed significantly less postoperative sickness in the first 1 h after surgery than a control group; only invasive acupuncture remained effective after the first 1 h. Furthermore, the efficacy of these four methods was similar to either cyclizine 50 mg or metoclopramide 10 mg, given with the premedication. In a similar study, Dundee, Milligan and McKay [20] reported that P6 acupuncture was less effective than droperidol 2.5 mg as a postoperative antiemetic.

There are only two studies of P6 stimulation in adults which are comparable to the work of Dundee's group. The study by Fry [11] using acupressure has been discussed earlier. Weightman, Zacharias and Herbison [21] investigated the effect of P6 acupuncture, administered during surgery, in women undergoing elective laparoscopy. The patients were premedicated with oral temazepam, and morphine 0.1 mg kg^{-1} was administered during surgery. Anaesthesia was induced with thiopentone, and maintained with nitrous oxide and isoflurane in oxygen. The trachea was intubated, using vecuronium for neuromuscular block. There were no significant differences in the incidence of postoperative nausea and vomiting in the group of women receiving acupuncture, compared with an untreated group. The authors concluded that acupuncture, as used in their study, was unlikely to be a useful antiemetic for postoperative emesis. Dundee and Ghaly [22] have explained this failure to confirm their results in terms of the timing of acupuncture; to be effective as an antiemetic, acupuncture must be applied before the emetic stimulus.

The majority of studies investigating the effect of P6 stimulation on postoperative emesis have been conducted in women, undergoing minor gynaecological surgery. In this group of patients, both acupuncture and acupressure appear to be as effective as metoclopramide 10 mg and cyclizine 50 mg, but less effective than droperidol 2.5 mg. However, some of these antiemetics may be ineffective after a different surgical procedure or anaesthetic technique. In two separate studies, both acupuncture [21] and metoclopramide 10 mg [23] did not reduce the incidence of postoperative emesis in women undergoing elective laparoscopy. In the latter study, only droperidol 0.01 mg kg^{-1} significantly reduced postoperative emesis [23].

P6 stimulation (acupuncture and acupressure) appears to be a clinically useful, non-toxic antiemetic in certain groups of patients. The factors influencing its effectiveness have not been clearly defined, although gender, age, timing of P6 stimulation, type of surgery or emetic stimulus and anaesthetic technique may all be important. Several different emetic stimuli probably combine to produce a high incidence of postoperative vomiting in children undergoing outpatient surgery for correction of strabismus. In the present study we found P6 acupressure was ineffective as an antiemetic in this group of children.

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PREANAESTHETIC MEDICATION WITH CLONIDINE: A DOSE–RESPONSE STUDY

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SUMMARY

Eighty normotensive female patients were studied in a randomized, double-blind investigation, in which orally administered clonidine 0.1 mg, 0.2 mg and 0.3 mg were compared with a standard benzodiazepine premedicant. Clonidine 0.2 mg produced a significant reduction in anxiety ($P < 0.05$*) compared with all the other groups, and a better quality of induction of anaesthesia when compared with temazepam 20 mg and clonidine 0.1 mg. The decreases in arterial pressure and heart rate with clonidine 0.3 mg were significant compared with the other treatment groups. Hypotension persisted into the postoperative period after premedication with clonidine 0.3 mg, and this dose is not recommended as a routine premedicant.*

KEY WORDS

Complications: hypotension Premedication clonidine, benzodiazepines

There has been considerable interest in the alpha-2 adrenergic agonists [1]; they have been shown to have properties that are of potential benefit in premedication [2, 3]. Although newer and more selective agents are being used with some success in both animal and volunteer studies [4], clonidine, while not a pure alpha-2 adrenergic agonist, is the only clinically available agent in this drug group. Their central actions reduce sympathetic activity, producing sedation, anxiolysis, drying of secretions, with a reduction in the requirement of anaesthetic agents [5] and improved cardiovascular stability in the perioperative period [6]. More recently, clonidine has been shown to have potential as an analgesic when administered by the extradural or intrathecal route [7]. In a preliminary study [8] oral clonidine 0.3 mg produced significant anxiolysis and pleasant sedation when compared with a placebo, but with a concomitant reduction in arterial pressure and heart rate. The results indicated a dose–response study to assess the effects in a healthy population, and the influence on a standard anaesthetic sequence.

In this study, we have examined the effectiveness of clonidine as a premedicant, using a range of doses to determine if anxiolysis and sedation may be combined with minimum cardiovascular effects. Temazepam was included as an active control.

PATIENTS AND METHODS

The study was approved by the local Ethics Committe and informed consent was obtained from all patients. We studied healthy women undergoing minor gynaecological surgery under general anaesthesia (weights 45–95 kg; ages 18–65 yr). At the preoperative visit on the evening before surgery, the Visual Analogue Scale (VAS) for anxiety was explained to the patient, who then recorded a baseline score, using a 100-mm scale with 0 = completely calm and 100 = worst possible anxiety. Arterial pressure and heart rate were recorded. Premedication consisted of either clonidine 0.1 mg, 0.2 mg, 0.3 mg or temazepam 20 mg, and was administered orally 60–90 min before surgery. The treatment distribution was double-blind and randomized.

Sedation was assessed by one blinded observer (author), on arrival in the anaesthetic room, using a three-point scale: awake and alert, awake but

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TABLE I. *Patient characteristics (mean (range or SD))*

	Group A ($n = 20$)	Group B ($n = 20$)	Group C ($n = 20$)	Group D ($n = 20$)
Age (yr)	35.4 (21–51)	41.5 (24–61)	41.5 (26–57)	33.7 (19–51)
Weight (kg)	59.1 (8.2)	66.6 (11.5)	61.1 (13.1)	60.1 (12.3)

uncommunicative, and drowsy. The patient completed a second VAS for anxiety. Spontaneously volunteered side effects were noted.

A suitable vein was cannulated and arterial pressure and heart rate measured using an automated oscillotonometer and ECG. Further cardiovascular measurements were made at 1-min intervals for 8 min after induction, before the onset of surgery and at 5-min intervals during the operation and into the recovery period. Oxygen saturation was monitored throughout, using a pulse oximeter.

Anaesthesia was induced using etomidate 0.2 mg kg^{-1} administered over 15–20 s; no supplementary doses were required. Patients were allowed to breathe spontaneously 60% nitrous oxide and 1.5% isoflurane in oxygen for 8 min before the onset of surgery, via a Bain system with a fresh gas flow of 1.5 times the minute volume. The concentration of isoflurane was maintained at 1.5% during the study. The quality of induction was assessed on a four-point scale: 1 = smooth; 2a = mild brief hiccup or involuntary movement; 2b = moderate hiccup or laryngospasm or involuntary movement lasting up to 30 s; 3 = unacceptable upset.

Emetic sequelae were recorded as either early (in the first 2 h) or late (from 2 to 24 h).

Results are presented as mean (SEM) for parametric data, and median with range for non-parametric data. Data were analysed by Kruskall–Wallis and Mann–Whitney *U* test for non-parametric data. Parametric data were analysed using ANOVA and Student's *t* test. $P < 0.05$ was deemed significant.

RESULTS

Eighty patients were studied in four groups of 20: group A clonidine 0.3 mg, group B clonidine 0.2 mg, group C clonidine 0.1 mg and group D temazepam 20 mg. The groups were comparable in weight and age; the duration of the surgery did not exceed 15 min (table I).

Patients noted to be sedated were easily roused and no patient was assessed as too drowsy to complete the VAS for anxiety (table II). Sedation with clonidine increased with increasing dose, but none of the differences was significant. Pre-induction anxiety was significantly less in the clonidine 0.2 mg group compared with the other groups ($P < 0.001$). Temazepam did not produce better sedation or anxiolysis than any clonidine treatment.

All the inductions graded as unsatisfactory were on the basis of involuntary muscle movement. Only one patient in group B had an unsatisfactory induction, compared with seven in group C ($P < 0.05$) and six in group D ($P < 0.05$). There was no difference in the quality of induction of anaesthesia between groups A and B (table III).

Arterial oxygen saturation did not decrease to less than 95% in any group. Arterial pressure and heart rate measurements were comparable

TABLE II. *VAS scores for anxiety before and after premedication (mean with range) and sedation scores before induction (percentage values).* *$P < 0.05$ *compared with other groups*

	Clonidine			Temazepam
	0.3 mg	0.2 mg	0.1 mg	20 mg
VAS score				
Before premed.	29 (0–85)	30 (2–75)	32 (5–80)	29 (0–75)
After premed.	35 (5–100)	15 (2–49)*	41 (0–95)	32 (4–100)
Sedation				
Awake/alert	25	20	45	35
Awake/uncommunicative	40	60	45	50
Drowsy	35	20	10	15

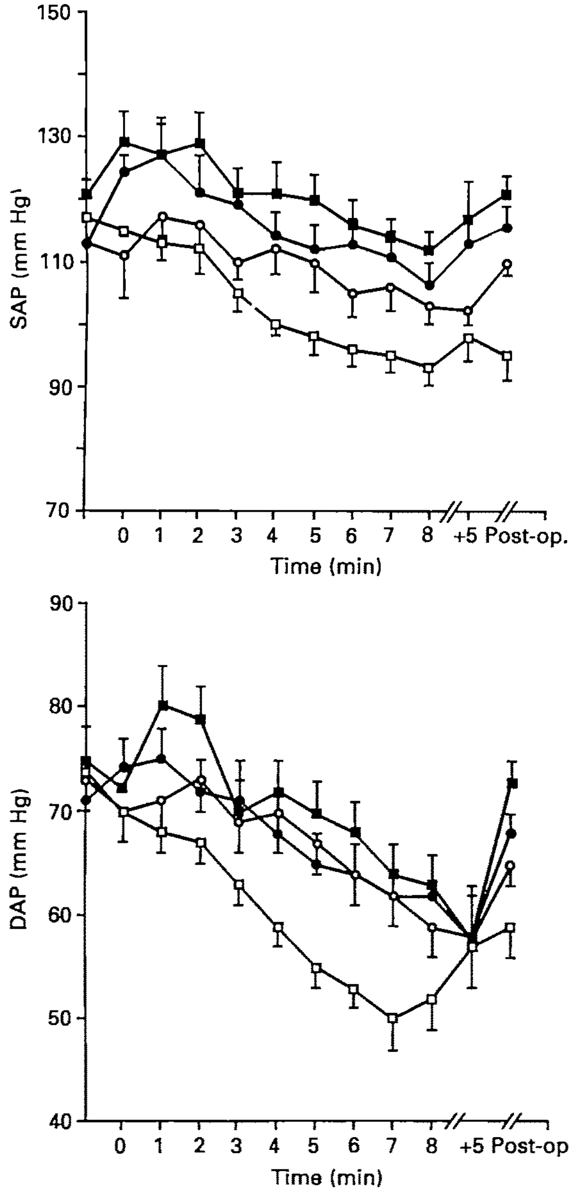

FIG. 1. Systolic (SAP) and diastolic (DAP) pressures (mean, SEM) in the four groups: clonidine 0.3 mg (□); clonidine 0.2 mg (○); clonidine 0.1 mg (■); temazepam 20 mg (●). 0–8 min = assessment period; +5 min = intraoperative value; Post-op. = 30 min after operation.

TABLE III. *Quality of induction*

Grade	Group A ($n = 20$)	Group B ($n = 20$)	Group C ($n = 20$)	Group D ($n = 20$)
1	11	11	7	5
2a	5	8	6	9
2b	4	1	5	5
3	0	0	2	1

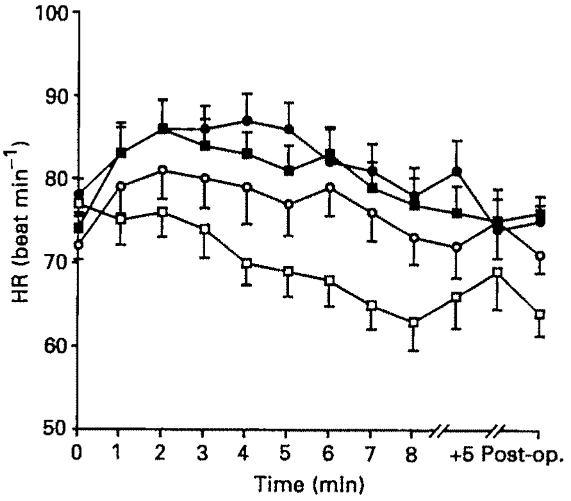

FIG. 2. Heart rate (HR) (mean, SEM) in the four groups: clonidine 0.3 mg (□); clonidine 0.2 mg (○); clonidine 0.1 mg (■); temazepam 20 mg (●). 0–8 min = assessment period; +5 min = intraoperative value; Post-op. = 30 min after operation.

on the ward (figs 1, 2). Induction of anaesthesia did not alter systolic pressure unduly, and the values at 1 and 2 min were not significantly different between groups. As anaesthesia was established with the inhaled mixture of nitrous oxide and isoflurane, there was a trend for a decrease in systolic pressure. Compared with baseline values, systolic arterial pressure was significantly less in group A from the 3rd minute of the study period to the onset of surgery and, after operation, two patients required i.v. fluids for hypotension in the recovery ward. The downward trend in group A was significant compared with groups C and D ($P < 0.05$), on analysis of both the slopes of the data and the values. There were no significant differences between groups B, C and D, although in group B the systolic pressure was reduced significantly compared with baseline 7 and 8 min after induction. The diastolic pressure followed a similar pattern, and group A demonstrated a significant decrease in both values and trends compared with the other groups.

The heart rate changes in group B, C and D were not significant on within- or between-group comparisons. In group A, the heart rate decreased significantly compared with both the other groups and baseline values from the 3rd minute of the study period until the onset of surgery ($P < 0.05$).

Nausea and vomiting occurred only in the initial postoperative period. Group A and B had three and two patients, respectively, with emetic symptoms, compared with six patients in each of groups C and D (not significant).

DISCUSSION

We have confirmed that sedation with clonidine was dose related, increasing with the dose [9], and was as effective as temazepam, a commonly used premedicant noted for its sedative properties [10]. While all patients exhibited a similar degree of anxiety at ward interview, only those given clonidine 0.2 mg displayed reduced anxiety immediately before induction. This highly significant difference is difficult to explain. Using clonidine 0.3 mg, Pouttu and colleagues [11] did not demonstrate anxiolysis, whereas Wright and co-workers [8] using a similar dose, showed significant benefit compared with an inert treatment. The different anxiolytic properties demonstrated between the clonidine groups resembles the "therapeutic window" description of the hypotensive action [12]—namely, that large and small doses produced less effect on arterial pressure [13]. Recent evidence has demonstrated that the analgesic properties of clonidine are attributable to a central alpha-2 adrenergic mechanism [14], while cardiovascular changes are caused by a combination of effects on central alpha-2 and peripheral alpha-1 and alpha-2 receptors [15]. Alpha-2 adrenergic effects are more pronounced at smaller doses, while with large doses alpha-1 effects predominate. The differeing degrees of anxiolysis reported here may be caused by a combination of effects at the alpha receptors.

Etomidate is an induction agent which is associated with a high incidence of involuntary muscle movements and respiratory upset [16], which may be reduced by premedication with benzodiazepine and opioid drugs [17]. Increasing the dose of clonidine did not appear to alter the frequency of involuntary muscle movements noted at induction.

This investigation indicates that hypotension and bradycardia may be expected with larger doses of clonidine, particularly when combined with a potent inhalation agent. Although it has been suggested that premedication with this alpha-2 adrenergic agonist may improve cardiovascular stability during anaesthesia, our results for the larger doses do not support this. The findings agree with previous work by Wing, Reid and Hamilton [18] who demonstrated a 10–15% reduction in systolic and diastolic pressures in normotensive individuals after a dose of approximately 0.3 mg. The hypotensive effects are usually maximal 60–90 min after oral administration [19]. With larger doses, the hypotensive effects may persist [20] and preclude the use of clonidine as a routine perioperative drug. Although previous workers have shown a significant degree of bradycardia after clonidine 0.3 mg [21], no patient in this study required treatment for bradycardia.

Although clonidine is advocated as an adjuvant to anaesthesia, the use of this drug requires caution. In a dose of 0.2 mg, clonidine had an effect on arterial pressure and heart rate not significantly different from that of temazepam, and the anxiolysis produced was superior. These cardiovascular effects might usefully be harnessed to prevent "alpine anaesthesia" [22], and they may have a place for use in patients with limited myocardial reserve. However, on the evidence of this and our previous investigation, clonidine appears to offer no advantage over premedicants used currently.

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HALOTHANE HEPATITIS

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HISTORICAL BACKGROUND

Halothane was introduced into clinical use in 1956 and was hailed immediately as a great advance in anaesthesia [77]. Its advantages of potency, lack of flammability and general smoothness of administration led rapidly to widespread use. Initial animal studies indicated minimal or no hepatotoxicity [90, 130, 151, 174], and early clinical accounts of the use of halothane in man supported these studies [99, 135]. Reports of postoperative liver necrosis after the use of halothane began to appear in 1958 [19, 173] and further anecdotal reports followed [13, 18, 97, 158]. By 1963, 5 years after the widespread international use of halothane, at least 350 cases of "halothane hepatitis" had been recorded [16].

Retrospective studies

The general concern precipitated a number of retrospective surveys of hepatic dysfunction following general anaesthesia, all of which found no greater incidence of liver damage after halothane anaesthesia than after other general anaesthetic agents [2, 38, 61, 89, 113, 126, 148, 161]. These reports led to the National Halothane Study, which reviewed cases of fatal hepatic necrosis occurring within 6 weeks of anaesthesia in 34 hospital centres in the U.S.A. [114]. Eighty-two cases of fatal hepatic necrosis were identified from some 856000 administrations of general anaesthesia, of which about 255000 involved halothane. In all but nine of these cases, the necrosis could be assigned to a recognizable clinical factor. Seven of these patients with unexplained liver necrosis had received halothane, and four of the seven had received halothane on more than one occasion within the previous 6 weeks. Thus the incidence of fatal hepatic necrosis following halothane anaesthesia in this study was approximately 1 in 35000. Weaknesses in the study design, however, may have prejudiced the results: the study was retrospective, although the original intention had been to establish a prospective survey, and reporting bias might have occurred, as some of the reporting institutions involved had already published anecdotal case reports of liver dysfunction associated with halothane. In addition, there was no information available on postmortem examination of the abdominal viscera in 40% of the deaths considered in the study. The main conclusions which emerged from this study were that postoperative massive hepatic necrosis was a rare occurrence, although an association with halothane could be neither confirmed nor excluded, and that halothane had a good overall record of safety, including use in operations involving the gall bladder and biliary tract.

Other retrospective studies confirmed that halothane was associated with severe liver dysfunction, with an incidence ranging from 1 in 6000 to 1 in 20000 [11, 72] and, in addition, it became apparent that there was a greater problem with repeated exposure to halothane, especially at short intervals. [11, 72, 73, 111, 176].

Prospective studies

Three small, but well-controlled, prospective studies of changes in liver biochemical tests after anaesthesia and minor surgery have been reported from Britain [46, 162, 185]. These showed that more liver enzyme abnormalities occurred after multiple exposures to halothane than after non-halothane anaesthesia, although other workers have published reports which do not confirm these findings [3, 104]. More recently, increased

KEY WORDS

Anaesthetics, volatile. halothane Complications· hepatic. Liver· hepatotoxicity.

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plasma concentrations of glutathione S-transferase (a sensitive and specific index of acute, drug-induced, hepatocellular dysfunction) have been demonstrated after halothane but not isoflurane anaesthesia [1, 70]. In a survey of postoperative complications, Zaric and colleagues encountered four cases of presumed halothane hepatitis in 2609 consecutive surgical patients, of whom 1166 were anaesthetized with halothane; no case of hepatitis was reported among the other patients, who had received enflurane, regional or i.v. anaesthesia. All four implicated patients were obese, middle-aged females, who underwent non-abdominal surgery, and three of the four had received halothane previously [186].

Most of these prospective studies, however, have described only altered liver enzymology and not the full clinical syndrome of halothane hepatitis.

EPIDEMIOLOGY

Several possible risk factors for the development of halothane hepatitis have become apparent on the basis of reported cases: multiple exposure, middle age, obesity, female gender, genetic predisposition and enzyme induction.

Multiple exposure

The risk of halothane hepatitis is increased greatly when repeated halothane anaesthetics are given over a short period [11, 72, 73, 111]. More than 80% of patients who develop hepatic necrosis after halothane have been exposed previously to the agent [160, 176] and up to 67% of patients who develop fulminant hepatic failure after halothane may have had a documented adverse reaction to halothane, such as postoperative pyrexia, nausea and jaundice [119]. Inman and Mushin reviewed 251 cases of alleged halothane hepatotoxicity reported to the Committee on Safety of Medicines [73]. Of these, 82% involved multiple exposure to halothane, and 75% of these patients had been exposed more than once within 28 days. Irrespective of the interval, multiple exposure was associated with a higher mortality (51%) than was single exposure (35%). Although the incidence of dysfunction appeared to be maximal when the penultimate exposure was within 28 days, cases have been reported when the penultimate exposure was several years previously [72, 119]. The shorter the interval between exposures, the more severe is the hepatic dysfunction and the shorter is the latency before presentation [73, 111, 119]. However, firm evidence does not exist to support the recommendation from the Committee on Safety of Medicines that repeat halothane anaesthesia should be avoided within 3 months.

Middle age

Middle-aged patients have a greater propensity to develop liver damage than the young or elderly [11, 20, 119, 176]; 70% of cases occur in patients older than 40 yr, and the peak incidence occurs between 50 and 60 yr. In comparison with the age distribution of patients undergoing anaesthesia, patients with halothane-induced liver disease are slightly older [11, 20, 119]. Severe hepatic dysfunction following halothane in children was not considered previously to be a hazard, but an increasing number of reports indicate that it can occur [82, 177, 179, 180, 181]. The incidence in children is, however, considerably smaller than in adults (between 1 in 82000 [177] and 1 in 200000 [180]).

Obesity

Hepatic dysfunction is more common in obese than in non-obese patients [20, 126, 176]. As halothane accumulates in adipose tissue, this could delay its excretion and, theoretically, prolong exposure to potentially reactive halothane metabolites, resulting in increased risk in obese patients. In addition, obese patients metabolize halothane more extensively than do non-obese patients [8], which might further predispose them to liver injury.

Female gender

Although there is no difference in exposure to halothane between the two sexes [20], females are at greater risk than males of developing liver injury by approximately 2:1 [7, 119]; nevertheless, male patients apparently have a worse prognosis [11, 111, 176]. Recently, Jenner, Plummer and Cousins have shown that reductive biotransformation of halothane was more extensive in females than in males undergoing routine anaesthesia, which might explain the association between female gender and halothane hepatotoxicity [75].

Genetics and ethnic origin

Susceptibility to halothane hepatitis may, to a certain extent, be heritable. Hoft and colleagues have reported cases of halothane hepatitis in three pairs of closely related women of Mexican–Indian or Mexican–Spanish descent [62], and a familial susceptibility factor may exist [43].

Enzyme induction

The association between hepatotoxicity and repeated exposure to halothane might be explained if halothane anaesthesia itself induced drug metabolizing enzymes. Halothane is known to cause microsomal enzyme induction in both adults [120] and children [60]. Further support for this hypothesis is provided by a study in which the incidence of liver injury was greater in subjects treated with phenobarbitone before halothane anaesthesia than in those not taking enzyme-inducing medication [121].

Other factors such as type of surgery and the presence of pre-existing liver disease might also be expected to influence the development of liver necrosis after halothane anaesthesia. However, no correlation between hepatotoxicity and duration, site or severity of surgery (including hepatobiliary procedures) has been shown in man [7], and in fact halothane hepatitis may follow apparently uneventful anaesthesia for minor surgery [119]. Similarly, there is no convincing evidence that patients with pre-existing, compensated liver disease are at any greater risk of developing halothane hepatotoxicity than healthy patients [15, 31, 153]. Radiation therapy in association with repeated exposure to halothane was considered previously to increase risk of hepatic damage [67], but subsequent studies have not been corroborative [3, 178].

Halothane hepatotoxicity is not restricted to patients undergoing anaesthesia. Liver damage following occupational exposure to halothane has been reported in medical personnel including anaesthetists, surgeons and laboratory workers [6, 76, 87, 98, 103, 118]; three of these individuals developed hepatitis following deliberate re-exposure to halothane, providing compelling evidence for the existence of halothane hepatotoxicity.

CLINICAL FEATURES

Halothane hepatitis is characterized by several consistent clinical features: non-specific gastrointestinal upset, delayed pyrexia, jaundice, eosinophilia, serum auto-antibodies, non-specific rash and arthralgia.

Many patients complain initially of malaise, anorexia and *non-specific gastrointestinal symptoms* such as nausea and upper abdominal discomfort [89, 111]. The onset of *fever* is characteristically the first sign of illness. Klion, Schaffner and Popper found pyrexia in 37 of 42 patients with presumed halothane hepatotoxicity, but only persistent or recurrent fever was related to the onset of hepatitis [89]. Moult and Sherlock described a pattern of delayed pyrexia after exposure to halothane in eight patients [111], and 75 % of patients in a series from King's College Hospital, London, developed unexplained fever after operation [119]. The mean interval between operation and onset of fever was 7 days after a first exposure, whereas multiple exposures were associated with a reduced latent period of 4 days [11]. Not all patients become pyrexial, however [176], and the value of unexplained postoperative fever as an indicator of sensitization to halothane has been questioned [36].

Jaundice occurs almost invariably. Many studies have shown that its appearance is delayed until the 5th or 6th day after exposure [73, 111, 119], although rarely it may be delayed by up to 4 weeks [89]. As with fever, multiple exposures to halothane are associated with a shorter delay in appearance of jaundice than that after a single exposure. In a series of 251 cases reported to the Committee on Safety of Medicines, patients became icteric after a mean delay of 11 days following a single exposure and about 4–6 days in instances of multiple exposures [73].

Eosinophilia is occasionally present, its incidence ranging from 8 % to 32 % [11, 89, 111, 176]. *Serum autoantibodies* are often found during the course of liver failure. Walton and colleagues found liver kidney microsomal antibodies in 19 of 76 patients with unexplained jaundice after halothane, with a similarly high incidence of thyroid antibodies [176]. Neuberger and Williams identified serum autoantibodies (antiliver kidney microsomal, antismooth muscle, and antinuclear) in 44 % of their patients [119]. A small number of patients may develop a *non-specific rash*, or *arthralgia* [176].

Biochemical tests of liver function generally reflect changes which are typical of hepatocellular damage. Serum transaminase activities are frequently grossly increased (500–2000 u litre^{-1}) [11, 89, 111], although the degree of increase may vary widely [176]. Alkaline phosphatase activity, although increased, is generally less than twice the upper limit of normal [176]. Clinically insignificant disturbances in liver biochemical tests are common following halothane, and to a lesser extent after enflurane. These alterations are not related to acute necrosis in an obvious spectrum, and have not been shown to have important sequelae [46].

PATHOLOGY

Light microscopy

The most notable histological feature of halothane hepatitis is centrilobular necrosis [7, 10, 89, 141, 148, 165, 183]. A spectrum of severity exists from panlobular and multifocal spotty necrosis through to massive necrosis. There is associated ballooning degeneration of hepatocytes, with subsequent inflammatory infiltrate, collapse and stromal fibrosis. Fatty infiltration has been noted also by several investigators [7, 10, 89, 97, 148]. Granulomatous aggregates are occasionally seen [7]. As many of these features occur in viral hepatitis, it may be difficult to distinguish between the two conditions on light microscopy, although a number of authors consider that such distinction can be made [7, 89, 126, 165].

Electron microscopy

Klion, Schaffner and Popper described mitochondrial membrane abnormalities as the most prominent feature seen on electron microscopy in halothane hepatitis [89]. Although these findings were confirmed by Uzunalimoglu, Yardley and Boitnott [165], other workers have noted only very mild or less frequent changes [141, 183]. More recently, Goldfarb and colleagues used electron microscopy to examine liver biopsy specimens taken during anaesthesia with halothane, isoflurane or droperidol [54]. No mitochondrial abnormalities were seen, but significantly more lysosomes were found in the hepatocytes of patients receiving halothane than in those receiving isoflurane or droperidol. It appears that halothane can induce ultrastructural abnormalities very early after the beginning of its administration, while, under the same conditions, isoflurane does not. However, as none of these patients subsequently developed clinically obvious liver damage, the relation of these ultrastructural changes to those seen in halothane hepatitis is not known.

AETIOLOGY

There are classically four major theories proposed to account for halothane hepatotoxicity: toxic products of metabolism, hypersensitivity, regional hepatic hypoxia and genetic predisposition. To these has been added more recently a fifth theory: that of altered hepatocellular calcium homeostasis.

Biotransformation

Halothane is metabolized in the microsomal fraction of the liver [167] via two main pathways (fig. 1): oxidative metabolism is greater in the presence of high oxygen tensions, while reductive metabolism is favoured by hypoxic conditions and phenobarbitone pretreatment. The extent of this metabolism is approximately 20% [131]. Both pathways exist in man and reductive metabolism is known to occur in patients undergoing routine halothane anaesthesia [30]. Metabolism begins soon after commencing the administration of halothane and continues into the period immediately after anaesthesia [4, 55].

Trifluoroacetic acid and bromide ion are the predominant products of oxidative metabolism [131, 152]; the major products of reductive biotransformation are 2-chloro-1,1,1-trifluoroethane, 2-chloro-1,1-difluoroethylene and fluoride ion [112, 142, 168]. Although none of the end products of either metabolic pathway has been shown to be toxic *per se*, intermediate products of biotransformation may be responsible for direct hepatic injury; it has been proposed that liver damage is mediated via reactive, free radical intermediates, as occurs with the classical hepatotoxins carbon tetrachloride and chloroform. Although free radicals are produced during administration of halothane [127], there is no direct evidence that they are responsible for halothane hepatotoxicity.

In 1969, Cohen demonstrated that non-volatile metabolites were bound covalently to liver macromolecules in mice for at least 2 weeks after halothane exposure, although this could not be correlated with hepatic necrosis as none was seen [27]. This binding was increased greatly in phenobarbitone-induced animals [17]. Binding occurs in the microsomal fraction of the liver [169] and depends on the transformation of volatile agents by the mixed function oxidase–cytochrome P450 system [81]. The extent of binding is enhanced by inducers of cytochrome P450, for example phenobarbitone [166], and is

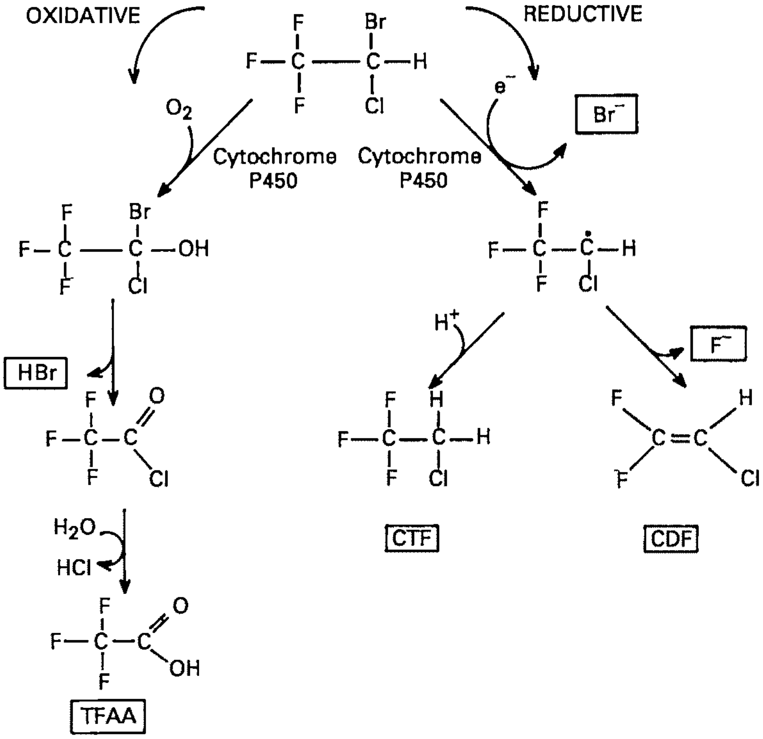

FIG. 1. Oxidative and reductive pathways of halothane metabolism. Major products of metabolism are enclosed in boxes. CTF = 2-Chloro-1,1,1-trifluoroethane; CDF = 2-chloro-1,1,-difluoroethylene; TFAA = trifluoroacetic acid.

reduced by enzyme inhibitors, such as metyrapone [47] and SKF 525A [169]. Covalent binding of metabolites increases under hypoxic conditions [163], although oxygen is required initially to convert halothane to the intermediate metabolite, which is bound [166]. Products from reductive metabolism are therefore thought to have more hepatotoxic potential than oxidative metabolites [47, 182] and for this reason much attention has focused on the role of reductive metabolism in mediating halothane hepatotoxicity. It has been hypothesized that $CF_3C^{\cdot}HCl$ free radicals are formed by cytochrome P450, and that some of these radicals then initiate lipid peroxidation in the endoplasmic reticulum; the damage produced by this process might be responsible ultimately for cell death [57].

Enflurane and isoflurane undergo considerably less metabolism than halothane during routine anaesthesia (2.4% [23] and 0.2% [63], respectively). Neither drug is subject to reductive metabolism, and neither produces free radicals [127]. Because the extent of metabolism of halothane, enflurane and isoflurane is directly related to the incidence of reported clinical hepatic dysfunction for these drugs, it is proposed that products of metabolism play an integral role in the production of halothane-induced liver injury.

Immune-mediated hepatotoxicity

Several features of halothane-induced hepatotoxicity point to hypersensitivity as a mechanism. These include the frequent association with multiple exposures [11, 72, 73, 111], the common history of drug allergy or atopy [20, 176, 186], the association with fever and eosinophilia [7, 89, 160], a history of previous adverse reaction to halothane [119], provocation of hepatitis by deliberate challenge in previously affected individuals [6, 87], and the demonstration of circulating autoantibodies [119, 136, 143, 176]. Apart from the positive challenge tests, however, none of these features can be considered unique to immune involvement.

Initial studies to detect evidence of hypersensitivity responses in patients with halothane hepatitis produced conflicting results [110, 124, 175]. In 1978, *in vitro* sensitization of leucocytes to liver homogenates prepared from rabbits exposed previously to halothane was demonstrated in patients with halothane hepatitis [172]. Circulating antibodies that bound to the surface membrane of halothane-altered rabbit hepatocytes were detected subsequently in about 75 % of patients in whom fulminant hepatic failure occurred after halothane anaesthesia [83, 115, 171]. These antibodies could not be detected in the serum of normal healthy controls, patients with other types of liver disease, or patients exposed to halothane with no liver damage. The antibodies were of the IgG subclass and not of the IgM subclass, suggesting that sensitization to halothane-altered liver cell components had occurred following an earlier exposure. The same antibodies were detected to a similar extent (16 of 23 patients) in patients with less severe hepatitis after halothane anaesthesia [84]. These antibodies have been identified as being cross-reactive with trifluoroacetyl (TFA) halide bound covalently to liver protein (anti-TFA antibody) [66].

The presence of these antibodies in serum has been proposed as a diagnostic marker of halothane-induced liver damage [116]. However, in some patients the antibodies did not appear until 8 weeks after exposure to halothane and it is not known if the antibodies are a cause, or merely arise as a consequence, of hepatic damage [35]. Furthermore, several problems with the assay have been discovered that were not recognized previously [106], and Spence has warned of the limited value of the antibody test in diagnosing halothane hepatitis [150]. A more recent tiered system of laboratory methods may, however, offer greater potential for an accurate diagnosis [59].

The theories of biotransformation and immune-mediation are not mutually exclusive. Halothane hepatitis may be initiated by a reactive metabolite that alters the surface structure of hepatocytes; in susceptible individuals these changes may induce an immune response and subsequent cytotoxicity. In contrast with the biotransformation theory which emphasizes reductive halothane metabolism, metabolism via the oxidative route is necessary for the expression of halothane-altered membrane antigen [117]. Oxidative metabolism of halothane proceeds via TFA halide ($CF_3CBrClOH$) [81]. This is a reactive metabolite which can bind covalently to cellular constituents [47, 86]. Endogenous liver protein is, in effect, changed from "self" to "non-self", thus becoming immunogenic. Antibodies are elicited against this non-self protein, creating an immune response. Using immunohistochemical staining with an antibody specific for the hapten, Satoh and colleagues detected trifluoroacetyl-conjugated macromolecules on hepatocytes isolated from rats exposed to halothane [139]. They concluded that TFA halide reacted directly with constituents of the plasma membranes, or with other cellular components which became incorporated into the plasma membranes. In fact, the microsomal fraction was found to contain the greatest concentration level of trifluoroacetyl-conjugated macromolecules, the major component of which was identified immunochemically as a phenobarbitone-inducible form of cytochrome P450. The results suggested that TFA halide was so reactive that it bound predominantly to the cytochrome P450 which produced it [140]. Subsequent studies, however, have established that this is not the dominant protein acetylated [65].

Kenna and co-workers have investigated the mechanism of neoantigen generation by testing liver microsomes from rats exposed to halothane for reactivity with patients' sera and also with an antiserum specific for the covalently bound TFA halide [86]. They characterized the drug metabolite–tissue protein neoantigens and found that the patients' antibodies recognized epitopes consisting of the TFA group plus associated structural features of the protein carriers, and not the TFA hapten alone. In the same year, results from studies in man indicated that humans exposed to halothane express liver neoantigens which are analogous to the halothane metabolite–protein neoantigens characterized previously in halothane-exposed animals [85].

Hepatic hypoxia

Much evidence now exists implicating an imbalance between oxygen supply and demand in the development of halothane-induced liver damage. Hypoxia in the absence of anaesthesia can cause centrilobular necrosis in phenobarbitone-treated rats similar to that seen after exposure to halothane [144, 145]. The region around the central vein has the least oxygen tension, as it is the last site in the liver lobule to receive oxygen and therefore might be most influenced by hypoxia. Hypoxaemia rarely occurs or persists during clinical anaesthesia and therefore is unlikely to be a determinant of liver damage in anaesthetized humans. However, local liver hypoxia resulting from an imbalance between oxygen supply and demand may be relevant: factors known to increase oxygen consumption such as barbiturate treatment and hyperthyroidism are associated with increased halothane hepatotoxicity in the rat [105, 138, 149, 184].

Hepatocellular necrosis can result also from a decrease in oxygen supply secondary to reduced hepatic perfusion. In man, total liver blood flow is derived from two sources, the hepatic artery which supplies roughly 33% of the total flow but 50% of the oxygen supply, and the portal vein [157]. Normally, there exists reciprocity between hepatic arterial and portal venous flows, so that total liver blood flow tends to remain fairly constant [134]. Specific volatile anaesthetic agents have different effects on this reciprocity of flow. Halothane has been shown to decrease both portal blood flow and hepatic arterial blood flow [50, 52, 68, 69], although the reduction in hepatic arterial blood flow is somewhat inconsistent [49]; the main determinant of hepatic blood flow during halothane anaesthesia is cardiac output [50]. Enflurane decreases portal blood flow and, when administered in sufficient concentration to cause a 50% reduction in cardiac output, also impairs hepatic arterial blood flow [68]. It does, however, preserve liver blood flow and oxygen supply better than halothane when used in equipotent doses. In contrast, although isoflurane decreases portal blood flow, hepatic arterial blood flow increases, resulting in little change in total liver blood flow [50, 51].

It would appear therefore that, although all three volatile agents decrease portal blood flow, isoflurane and to a lesser extent enflurane facilitate oxygen delivery to the liver much better than halothane, mainly by a more effective preservation of hepatic arterial blood flow.

Pharmacogenetics

Evidence of a genetic basis for susceptibility to halothane hepatitis has been provided by several studies. The extent to which an individual metabolizes halothane, particularly via the reductive pathway, may be determined genetically [22, 102]. Further evidence of possible genetic determination was provided by a report of halothane hepatitis occurring in three pairs of closely related women of common ethnic origin [62]. In addition, a predisposing, familial, constitutional susceptibility factor may exist [43] and human lymphocyte antigen frequencies were found to be different in patients with halothane hepatitis compared with healthy controls [123]. Available evidence seems, however, to indicate that halothane-associated liver damage is more likely to be of multifactorial origin, of which pharmacogenetics constitutes, at most, one variable [14, 15].

Altered calcium homeostasis

It has been proposed that hepatic damage induced by volatile anaesthetic agents occurs secondary to disruption of mechanisms which maintain cellular calcium homeostasis [53]. Free, ionized, intracellular calcium concentration is in the range 100–200 nmol litre^{-1}, but that in extracellular fluid is upwards of 1 mmol litre^{-1} [129, 159]. Maintenance of this large chemical gradient is vital to cell viability; thus it is conceivable that processes leading to cellular injury may include alterations in calcium homeostasis. The gradient is maintained by a low natural permeability of the plasma membrane to calcium, the binding of cellular calcium to intracellular components, and the activity of at least two ATP-dependent transport mechanisms in the plasma membrane [24, 91]. In addition, both endoplasmic reticulum and mitochondria can actively sequester calcium from the cytosol, protecting the cell against calcium overload in times of excessive calcium transfer into the cell [5].

Calcium ions are thought to play a major role in mediating or propagating hepatocellular injury [42, 159]; it has been suggested that increased concentrations of free intracellular calcium constitute the final common pathway of cell injury [24]. Several known hepatotoxins increase cytosolic calcium [12, 108, 109]. Halogenated hydrocarbons may increase liver calcium by inhibition of a microsomal calcium pump [108] or by impairing the activity of endoplasmic reticulum [12, 100]. Specifically, halothane can inactivate irreversibly calcium transport in hepatic endoplasmic reticulum, provoking an immediate release of calcium [187].

Animal studies have provided evidence supporting a role for altered calcium fluxes in the mechanism of halothane-induced liver injury. In guineapigs, hepatic calcium content was increased significantly 24 h after exposure to halothane [44]. Subsequent changes in liver calcium were proportional to the severity of liver necrosis, as determined morphologically. The increase in liver calcium occurred before hepatocellular necrosis was observed histologically. This antecedent relationship of altered cellular calcium homeostasis to liver necrosis is consistent with a pathogenetic role in the production of liver injury. More recently it was shown that halothane, enflurane and isoflurane each stimulated a significant, dose-dependent release of radio-labelled calcium from internal calcium stores in isolated rat hepatocytes [71]. Halothane produced the greatest calcium release, and isoflurane produced the least—a pattern which is consistent with the known ability of these anaesthetics to induce hepatic necrosis.

Further evidence in support of the calciogenic hypothesis of cell injury is offered by studies in which the administration of a calcium channel blocker reduced the extent of hepatic necrosis in animals exposed to hepatotoxic agents, including halothane [48, 92, 107]. Clearly, calcium plays a major role in chemically induced cell injury, although the consequences of increased concentrations of cytosolic calcium remain incompletely understood.

Current perspectives

It is now recognized that two types of halothane-induced hepatic dysfunction exist [16, 119, 128, 160]. A mild subclinical form manifest by abnormal biochemical indices of hepatic function may occur in up to 20% of patients exposed to halothane. This could be caused by toxic products of halothane metabolism, possibly determined by genetic factors, or by hepatic hypoxia resulting from an imbalance between hepatic oxygen supply and demand. Altered hepatocellular calcium balance cannot be excluded as a possible mechanism. A much rarer fulminant form may occur with severe necrosis which may prove fatal. It is probable that this form results from an immune reaction: an oxidative metabolite binds covalently to liver proteins, producing a hapten which in turn provokes an immune reaction and the formation of a circulating antibody.

Precise definition of the mechanism(s) responsible for damage is complicated because no diagnostic test is available for either form of toxicity. Evidence exists supporting the involvement of each of the currently proposed aetiologies. For example, the extent of metabolism of halothane, enflurane and isoflurane correlates directly with the incidence of reported clinical hepatic dysfunction for these drugs, as does the degree to which each of these agents interferes with the balance between hepatic oxygen supply and demand, the extent to which each of them stimulates the release of calcium from stores in hepatocytes, and their ability to form immunoreactive protein adducts.

Hepatotoxicity following all volatile halogenated anaesthetics may be linked by a common mechanism. Christ and colleagues demonstrated that enflurane and isoflurane are converted to reactive metabolites that form covalently bound, acylated protein adducts which are recognized by specific anti-TFA antibodies [26]. Immunoblotting techniques used by the same group showed that antibodies in the sera of six patients with halothane hepatitis recognized liver microsomal antigens formed in rats treated with enflurane or halothane [25]. This suggested that a halide metabolite of enflurane bound covalently to liver proteins and could similarly provoke an immune response. This mechanism could account also for the apparent cross-sensitization between halothane and enflurane. Isoflurane did not produce detectable liver antigen, although the principal reason for this may have been related to the level of biotransformation in their particular animal preparation. However, isoflurane, enflurane and halothane all have the potential for producing acetylating intermediates that can alter liver proteins, rendering them immunogenic. Thus a common mechanism for producing liver damage may exist between the volatile halogenated anaesthetics.

ANIMAL STUDIES

Early attempts to produce an animal model of halothane hepatitis proved disappointing. Since 1976 however, five animal models have been developed, in each of which massive hepatic necrosis was produced.

Polychlorinated biphenyl rat model

Sipes and Brown described a rat model in which hepatic necrosis was induced by a single exposure to 1% halothane in 99% oxygen following pretreatment with Aroclor 1254, a polychlorinated biphenyl (PCB) [147]. PCBs are potent inducers of a wide variety of biotransformation pathways, but unfortunately can themselves cause liver damage [17], so this model is probably not appropriate.

Phenobarbitone—hypoxia rat model

Certain strains of male rats developed hepatic necrosis when exposed to halothane under hypoxic conditions after phenobarbitone pretreatment [32, 105, 138]. Both hypoxia and phenobarbitone are required to cause necrosis. As the severity of damage correlated with the amount of inorganic fluoride produced, it was proposed that the liver damage was mediated through reductive metabolism of halothane. This hypothesis was supported by Jee and colleagues, who found that the administration of the biotransformation inhibitors metyrapone and SKF 525A inhibited hepatic necrosis even when administered up to 4 h after anaesthesia [74].

Triiodothyronine rat model

Hepatic necrosis occurs in rats pretreated with triiodothyronine (T_3) and then exposed to halothane in non-hypoxic environments [149, 184]. Because the necrosis is caused in the absence of hypoxia, reductive metabolism is not implicated. In contrast to the phenobarbitone–hypoxia model, it appears that a mechanism other than reduction of halothane may be involved in the T_3 model [164]. It is proposed that hypoxic damage to the hypermetabolic centrilobular cells resulting from depression of splanchnic blood flow is responsible for the liver cell necrosis [9].

Isoniazid rat model

Rats pretreated with isoniazid and then exposed to halothane in air are also reported to develop hepatocellular necrosis [133]. As isoniazid treatment enhanced oxidative but not reductive halothane biotransformation, it was suggested that oxidative metabolism was responsible for hepatotoxicity in this model.

Guineapig model

More recently, a model has been described in which halothane produced hepatic damage in an outbred strain of guineapig [101]. Neither enzyme induction nor hypoxia was required for this effect. Subsequently, liver necrosis was described in certain other strains of guineapig [94]. Unlike other animal models, in which all animals developed severe centrilobular necrosis within hours of exposure, only 30% of guineapigs show a similar degree of severity. In addition, the development of necrosis is delayed for 48–72 h, and both sexes are affected. Although both reductive and oxidative metabolism of halothane occur in the guineapig it is the oxidative pathway which has been implicated as a mechanism of hepatic injury [95]. The guineapig has also been used to study the potential contribution to liver damage of a halothane-induced immune response [146].

How relevant these animal studies are to the problem of human hepatotoxicity is not known. The lesion in man is rare and unpredictable and animal models have not been in keeping with this clinical picture [29]. All three rat models require the presence of demanding conditional factors which would not be expected to pertain to man. These rat models display considerable sex, age and strain differences regarding susceptibility to hepatic necrosis. In addition, the phenobarbitone–hypoxic rat model shows a dose–response relationship [74], which is not the case in man, and hepatic dysfunction does not increase with multiple exposures [132]. In contrast, the guineapig model more closely resembles clinical observations in humans with regard to halothane biotransformation and lesion morphology [94], possible genetic predisposition [102] and induction of an immune response following multiple halothane exposures [146]. Therefore, although the animal models have enabled an understanding of some of the issues involved, they have not greatly advanced the quest for the cause of halothane hepatotoxicity in man.

OTHER INHALATION ANAESTHETIC AGENTS

Enflurane

There is not the same concern regarding hepatotoxicity after anaesthesia with enflurane as there is with halothane. Nonetheless, a few case reports of alleged enflurane hepatitis have been published [33, 34, 88, 122, 125]. In several of these reports, however, other causes of liver damage, such as viral hepatitis, could not be excluded. In a review of 58 cases of suspected enflurane hepatitis, Lewis and colleagues considered that 24 could be explained only as a result of the administration of enflurane [93]. Analysis of these cases demonstrated that the clinical, biochemical and histological features were similar to those seen with halothane-induced hepatitis. However, the vague and non-specific criteria for ascribing hepatotoxicity in that review have been criticized [37]. Furthermore, Eger and co-workers reviewed 88 cases of hepatic injury attributed to enflurane, including the material reviewed by Lewis, and could demonstrate neither a causal relationship between enflurane anaesthesia and subsequent liver injury, nor consistent histological changes in liver specimens [41].

It cannot be denied that unexplained severe liver damage follows enflurane anaesthesia in the rare patient: the known incidence is of the order of 1 in 800000, which is less than the spontaneous attack rate of viral hepatitis [16]. This incidence is too low to suggest a causal association and, in addition, a molecular mechanism by which enflurane might produce hepatotoxicity analogous to that produced by halothane is difficult to propose and support experimentally. There are few, if any, parallels between the metabolisms of halothane and enflurane, and the pattern of enflurane hepatitis does not tend to support an immune-mediated mechanism [41]. However, Christ and colleagues have suggested a possible hypersensitivity basis for enflurane hepatitis, involving the covalent binding of an oxidative metabolite to liver microsomal adducts [26]. The case for enflurane hepatitis currently remains "not proven", but further studies such as that undertaken by Christ may add weight to the argument for its existence.

Isoflurane

Two case reports have been published attributing hepatic injury to isoflurane, but in neither report did the results show a definitive causal relationship between isoflurane and liver dysfunction [21, 56]. Stoelting and colleagues reviewed 45 cases of hepatic dysfunction after isoflurane anaesthesia reported to the Food and Drug Administration in the United States of America [155]. They concluded that causes other than isoflurane could account for the postoperative liver damage in 29 patients while, in the remaining 16, isoflurane might have been one of several possible causes of injury. Current evidence suggests that it is highly unlikely that isoflurane is even rarely responsible for postoperative hepatotoxicity [154].

Sevoflurane and desflurane

More recently two other volatile agents, sevoflurane and desflurane (I-653), have attracted attention as alternatives to those presently available. Original animal studies suggested that servoflurane was not hepatotoxic [28], but subsequent investigations do not support this; it may cause hepatic injury of a degree similar to that associated with isoflurane in enzyme-induced hypoxic rats [156], and its administration to guineapigs also may result in liver damage [96]. Desflurane is a new volatile anaesthetic agent structurally very similar to isoflurane, which is currently being evaluated for clinical use [78, 79]. It has not been reported to cause hepatic injury in animals [39, 40, 64], or to influence biochemical tests of liver function in human volunteers [80].

Nitrous oxide

Nitrous oxide also has been reported to cause centrilobular necrosis in a rat model [45] and to potentiate the hepatotoxicity of halothane [137]. There is one human report of jaundice following anaesthesia in which the only inhalation agent used was nitrous oxide [58], although it is more likely that halothane was responsible for the jaundice, resulting from inapparent circuit contamination [170].

SUMMARY

The historical background, clinical features, morphology, epidemiology and aetiology of halothane hepatitis have been presented. Animal models of halothane hepatotoxicity have been described, although their application to humans is of doubtful significance. Two, probably distinct, forms of liver damage associated with halothane have been identified. The much more common mild form may result from reductive biotransformation of halothane, possibly influenced by genetic factors, or reduced liver oxygenation, whereas the rare fulminant form is most likely to be immune-mediated. The role of altered calcium homeostasis has not yet been established. In addition, a common mechanism for liver dysfunction associated with halogenated volatile anaesthetic agents has been proposed. The hepatotoxicity of enflurane cannot be excluded; while hepatic dysfunction after isoflurane or nitrous oxide is considered unlikely, further attention is necess-

ary. It is too soon to comment on the hepatotoxic potential of sevoflurane or desflurane.

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FIBREOPTIC SENSORS IN CLINICAL MEASUREMENT

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Measurement systems utilizing optical fibres are now becoming available for use in many different fields. Applications in clinical measurement are often cited in the scientific journals, as the small size and electrical safety of these optical devices make them potentially suitable for *in vivo* use within the blood stream and other body cavities [9, 13, 16, 20].

Many of the systems for clinical use are still at an experimental stage, and little information has filtered through to the clinical journals. This review outlines the basic principles of optical fibre sensors, and describes briefly how some of the variables of interest to the anaesthetist can be measured. A glossary of terms that may be unfamiliar to clinicians but are standard within this field is included as an Appendix.

OPTICAL FIBRES

Optical fibres are made of glass or plastic. A core section is encased in a cladding of material of lower refractive index, the whole having a diameter of about 0.1–0.2 mm. The principle of operation is shown in figure 1. Light from a bulb, laser or other device is directed into the fibre (the incident light), and is prevented from leaving the core by total internal reflection at the interface between the core and the cladding. The light is thus guided along the length of the fibre.

Some losses of light do occur, as a result of manufacturing tolerances and molecular interactions, but this is not usually a problem with the short lengths of fibre used in biosensors.

Optical fibre sensors may be classified into two broad groups according to the function of the fibres:

(1) The fibres may be used solely to transmit light to or from a remote location. In this arrangement, the fibres are analogous to wires carrying electrical data signals to and from the measurement site. Such an arrangement is termed an "extrinsic" system, and most of the sensors for biomedical use are of this type (fig. 2). (An ECG may be considered an extrinsic device, as the wires carry the small voltages generated by myocardial activity to a distant recorder.)

(2) If the variable to be measured may be made to interfere directly with the fibre to change its light-guiding properties, the fibre becomes an integral part of the system, rather than only a means of transmitting data. This arrangement is termed an "intrinsic" system (fig. 3). (A more familiar example of this arrangement would be a resistance thermometer, in which changes in ambient temperature alter directly the electrical resistance of the wires.)

In order to use intrinsic or extrinsic sensors in measuring systems, changes in the variable to be measured must result in some change in the characteristics of the light travelling along the fibre [5, 11].

Intensity

Changes in the intensity of the light are easy to measure, but a reference signal must be provided to negate the effects of drift.

Wavelength

Changes in the wavelength of light (i.e. colour), are also easy to measure spectrophotometrically. Many chemical indicators are available which change their colour in response to a change in concentration of some variable such as H^+ (pH). Haemoglobin saturation may be monitored in a similar way.

Changes in the intensity or colour of the light are the most common in biosensors.

KEY WORDS
Measurement techniques: fibreoptic sensors

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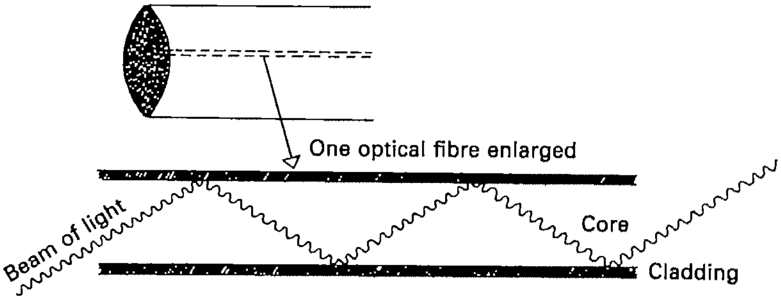

FIG. 1. Optical fibre. The refractive index of the cladding is less than that of the core.

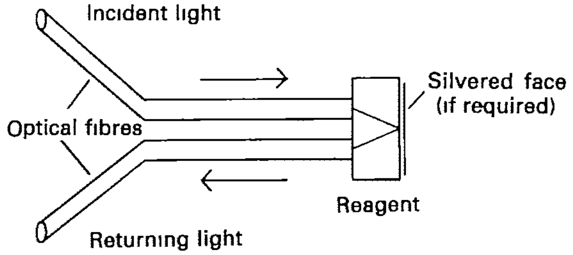

FIG. 2. Extrinsic sensor. The optical fibres are used solely to guide the light which is modulated by an external, optically active material.

Polarization

If the light source emits polarized light, and the variable to be measured is able to change the angle of polarization, this change in angle may be converted to variations in intensity using a plain polarized filter. (Polaroid sun-glasses work in this way to reduce the intensity of the partially polarized light produced by reflection from a surface such as water.)

This is a very sensitive technique, but it is difficult to use outside the laboratory because the angle of polarization may change as a result of physical stresses on the fibre.

Phase

The phase of the light may be measured using an interferometer. This is another highly sensitive technique that is probably unsuitable for use outside the laboratory, because of the problems of stability and calibration.

SENSOR DESIGN

The term "sensor" rather than "transducer" is used to describe these devices, as it does not imply a specific mode of operation (see glossary). Many of these devices are not transducers because no net energy transfer is involved.

For intravascular use, it is often most convenient to arrange fibres carrying incident and returning light to lie parallel with each other within an outer wrap. Some sensor designs involve transmission of the light through a reagent, rather than reflection of the light from the face of the material. In such designs, the distal face may be silvered, so that the light is reflected back again through the reagent to the returning fibre (fig. 2). A detailed account of the various factors and problems involved in sensor design may be found in references [1] and [22].

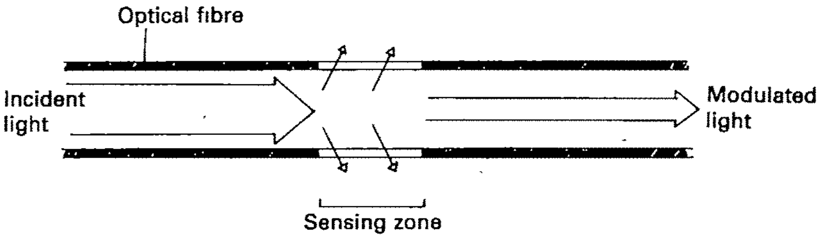

FIG. 3. Intrinsic sensor. Part of the cladding is replaced by a material the optical properties of which depend upon the surrounding medium.

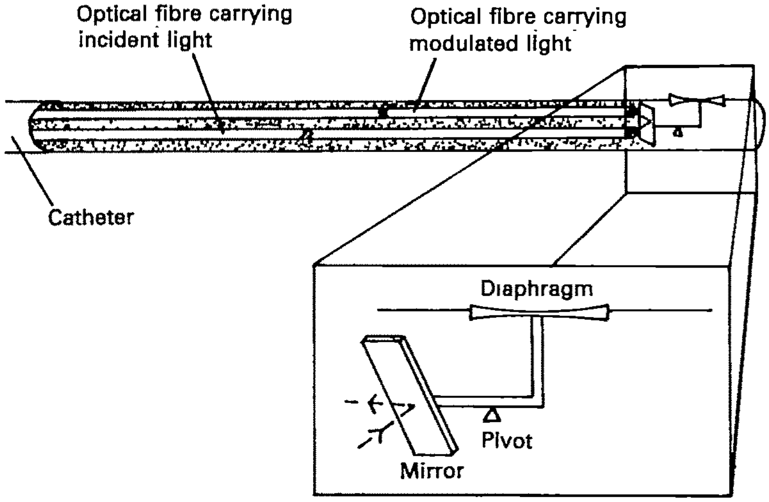
Optical fibre carrying incident light
Optical fibre carrying modulated light
Catheter
Diaphragm
Pivot
Mirror

FIG. 4. Pressure sensor. Extrinsic pressure sensor using a diaphragm and mirror to vary the proportion of incident light that is reflected into the returning fibre.

Sensors for Chemicals

These sensors are generally extrinsic. They may be classified into two types: those that utilize reversible chemical indicators, and those that utilize reagents which, when excited by light of a suitable wavelength, fluoresce to a degree dependent on the chemical composition of the surroundings. In both categories, the reagent is bonded onto the end of a pair of fibres, one of which illuminates the reagent while the other transmits the returning light back to a colour- or intensity-measuring system.

$P\text{CO}_2$ and pH may be measured using a reversible indicator [6], whilst $P\text{O}_2$, volatile agents, K^+ and glucose may be measured using fluorescence techniques [10, 15, 18, 27].

The colour changes of haemoglobin may be monitored very simply, and flow-directed catheters with integral optical fibres are available to provide a continuous measurement of mixed venous oxygen saturation [14, 26].

Measurement of $P\text{CO}_2$ by infra-red absorption spectrophotometry is familiar to anaesthetists. Optical fibres may be used to guide the incident and returning infra-red light to and from the measurement site. No sampling tube is required, and the system functions as a mainstream type analyser, but without the usual bulky optics. Unfortunately, ordinary glass fibres do not transmit light in the infra-red region and special fibres (termed chalcogenide fibres) have to be used. At present, chalcogenide fibres are very expensive and fragile, and infra-red $P\text{CO}_2$ analysis using optical fibres is impractical [28].

Sensors for Biological Compounds

Sensors for biological compounds such as antibodies are now becoming available for laboratory use. Antibody–antigen reactions may be monitored optically by coating the antibody onto a fibre (often in place of part of the cladding, making an intrinsic sensor). Subsequent combination with the antigen changes the transmission properties and may thus be detected as a change in intensity [24].

Immunofluorescence techniques and luminescent enzymes may be used with optical fibres and have enabled highly specific extrinsic sensors to be made for many widely differing compounds, from ethanol to acetylcholine receptors [4, 19]. These techniques (generally known as immobilized enzyme systems) are already producing practical measurement systems for materials that previously required time-consuming laboratory assays.

Sensors for Physical Variables

Temperature

Temperature sensors are based on changes in fluorescence, absorption spectra or refractive index.

Some phosphor compounds fluoresce at an intensity dependent upon their temperature. Such

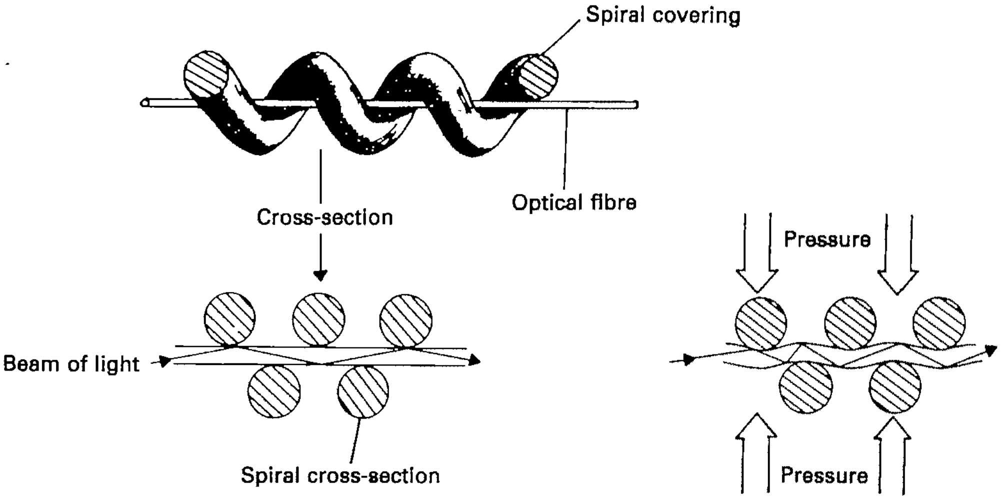

FIG. 5. Pressure sensor. A differential pressure across the spiral wrap deforms the fibre and disrupts total internal reflection of light at the core–cladding boundary.

a compound may be bonded to the end of a pair of fibres to form an extrinsic sensor in a manner similar to the fluorsensors described above.

Many materials change their light absorption spectra with temperature and may be bonded onto the end of a pair of fibres. The intensity of reflected or transmitted light of certain wavelengths varies with this temperature [2].

A small section of the cladding at the end of a fibre may be replaced by a compound in which the refractive index changes with temperature. The degree of reflection at the core–cladding interface (and thus the intensity of the light guided) then becomes temperature dependent, and the whole forms an intrinsic sensor [21].

Pressure

Until recently most systems for measurement of pressure were extrinsic, using a diaphragm and mirror assembly. A typical arrangement is shown in figure 4. The proportion of light reflected from one fibre back into the other is dependent on the angle of the mirror and thus on the pressure difference across the diaphragm. This design has been assembled within a catheter for measurements *in vivo* [12].

Other methods of pressure measurement have been tried, including sensors based on the change in polarization or phase of light passing through a material under stress. With some of these sensors the fibres constitute the material under stress, thus forming an intrinsic sensor [7, 17]. Another intrinsic pressure sensor may be based on microbending (fig. 5). The fibre lies inside a spiral cover. When pressure is applied to the spiral the fibre is deformed as shown and the total internal reflection properties are disrupted.

Flow

Fibreoptic sensors for flow are based on the principle of Doppler shift used in acoustic flow measurement. The optical version uses a laser light source and can detect flow velocities from 10^{-6} to 10^{5} m s^{-1} [23]. A spectrum analyser is used to detect the frequency shift. This forms an extrinsic sensor. At the present time, flow measurement systems based on this principle are not suitable for medical use, because of the requirement for a high degree of optical stability.

Flow may also be measured by exploiting the turbulence that occurs around a cylindrical object (fig. 6). A single fibre is placed across the flow, and small eddies are formed alternately on each side of the fibre (vortex shedding). Each eddy causes a small change in the pressure acting on the side of the fibre, causing it to vibrate laterally at a frequency dependent on the flow velocity. The vibrations result in a small loss of light from the core into the cladding, and the intensity of the light signal thus varies at the same frequency [5]. Sensors of this type may be suitable for use in anaesthetic breathing circuits.

A linear array of optical fibres mounted behind a variable orifice flowmeter may be used to

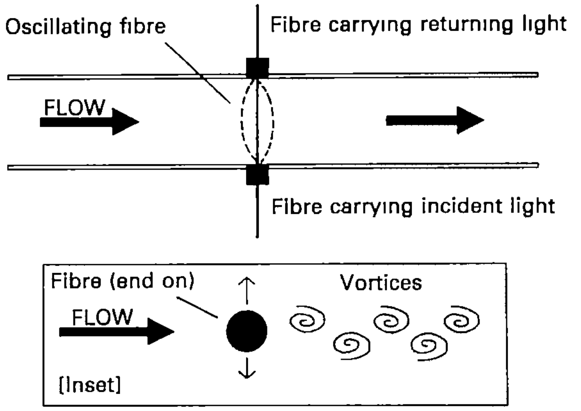

FIG. 6. Flow measurement. A fibre placed across the flow results in local turbulence and formation of eddies (vortices, see Inset). The asymmetrical formation of these vortices causes the fibre to oscillate.

monitor the position of the float and hence the flow rate. This is a simple technique and is directly applicable to the measurement of fresh gas flow rates in anaesthetic machines.

Optical versions of presently well established indirect techniques such as indicator dilution cardiac output measurement have been tried successfully. The fibres may be inserted down the lumen of a flow-directed catheter and measure the change in "colour" of the blood as the solution used as an indicator is injected [8, 25].

ADVANTAGES AND DISADVANTAGES OF FIBREOPTIC SENSORS

Typical sizes for some of the sensors described are shown in table I. These sensors are non-conducting, therefore there is no risk of micro-shock with *in vivo* probes (and thus no requirement for strict electrical isolation techniques) and no interference from surgical diathermy. Although single optic fibres are fragile, the small bundles usually used in these systems are reasonably robust. In addition, breakage of a few fibres in the bundle is not important in these applications, as the reference signal is affected in the same way as the data. (Breakage of fibres is a problem in endoscopes, as each broken fibre results in a "hole" in the visual image.)

The further development of immobilized enzyme systems may produce sensors capable of measuring *in vivo* many of the substances now measured using laboratory assay techniques.

Response times for these sensors vary depending on the exact design of the sensor. Physical systems such as the mirror pressure sensor respond in a few milliseconds, whilst some of the chemical sensors may take several minutes to reach 90% response.

There are many technical problems yet to be solved, particularly those associated with biocompatibility and fibrin deposition for *in vivo* probes, before these sensors become available for widespread routine use [3, 22].

CONCLUSION

Fibreoptic sensors for use in clinical measurement are now becoming available commercially. With these new sensors, it is becoming possible to measure, within the body, some chemical concentrations and physical variables of interest to the anaesthetist. These systems may eventually replace many laboratory techniques, but many problems remain before these sensors become reliable for *in vivo* use.

APPENDIX

GLOSSARY

Sensor: Device giving a signal for detection or measurement of a property to which it responds. In this context, the term sensor is taken to imply all components of the measurement

TABLE I. *Typical sizes of some optical fibre sensors: the size refers to the part of the sensor that is in contact with the variable. For comparison, a 20-gauge i.v. cannula is 0.9 mm outside diameter*

Sensor	Diameter (mm)	Length (mm)
Pressure sensor utilizing a plastic under stress	3.7	8
Mirror system for pressure	5 (approx.)	10
Fluorescent and other "reagent" type sensors	< 0 .6	2
Thermochromic temperature sensor	1.5	10
Refractive index temperature sensor	0.8	8
LASER Doppler flow sensors	< 0.4	Only the tip lies in the vessel

system up to, but not including, any subsequent processing required to convert the light signal into a more easily interpreted format (for example a digital display).

Detector: Device for detection or demodulation of signals.

Refractive index: The ratio of the velocity of light in two adjacent materials.

Polarization: The restriction of the oscillations of light waves so that they have different amplitudes in different planes through the line of propagation.

Fluorescence: Visible or invisible radiation produced from certain substances by incident light of shorter wavelength.

LASER: Light source that emits an intense beam of monochromatic and highly coherent light (i.e. the phase is constant across the width of the beam). Acronym for Light Amplification by the Stimulated Emission of Radiation.

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ABSORPTION OF ISOFLURANE BY SILICA GEL

A. B. LUMB AND M. J. LANDON

SUMMARY

We have studied the capacity of the drying agent silica gel (SG) to absorb isoflurane from gas samples. When dry, SG was able to absorb 31 times its own volume of isoflurane vapour, which could be recovered almost completely from the SG by displacement with water vapour. However, we were unable to demonstrate any significant absorption of isoflurane by wet SG. Care must be taken, therefore, when using SG as a drying agent in the sampling line of an analyser during research involving volatile anaesthetic agents.

KEY WORDS

Anaesthetics, volatile· isoflurane. Equipment· silica gel.

Silica gel (SG) is a drying agent with many applications in anaesthetic research. These include drying of gas samples before analysis of systems sensitive to water vapour, such as paramagnetic or katherometer-based analysers. An evaluation of a system to measure functional residual capacity during anaesthesia which used SG to dry the gas inflow to the helium and oxygen analysers indicated that the SG was removing the isoflurane present in the spirometer circuit. We have therefore undertaken a study of the absorption of isoflurane by SG.

METHODS AND RESULTS

Approximately 25 g of silica gel (6–20 mesh, self indicating, BDH, Poole, England) which had been dried by heating to 115 °C for 2 h, was poured into a 35-ml disposable syringe barrel and retained by a bung pierced with a cannula. This was connected to the output of a TEC 4 isoflurane vaporizer (Ohmeda, Keighley) set to 2% and supplied with dry nitrogen at a flow rate of 550 ml min^{-1} (validated with a soap film bubble meter). Samples were taken every 5 min from both the inflow and outflow of the SG container, and the percentage isoflurane determined by gas chromatography against a standard prepared by addition of a known volume of liquid isoflurane to a fixed gas volume. Sampling continued until the outflow concentration was more than 95% of the inflow and the SG was then re-weighed. The experiment was repeated with the same conditions as above, but an increased nitrogen flow of 620 ml min^{-1}. Preliminary experiments had established that there was no detectable absorption of isoflurane by either the syringe and associated tubing, or a syringe containing anhydrous calcium chloride.

Despite a consistent inflow through the SG of approximately 2% isoflurane, none was detected in the outflow gas for 30 min with a flow rate of 620 ml min^{-1}, and 50 min with a flow rate of 550 ml min^{-1}. A sigmoid shaped curve showed gradual saturation of the SG, the curve being shifted to the left with the greater flow rate (fig. 1). In the first experiment the weight of SG increased by 8.2 g which is equivalent to 5.4 ml of liquid isoflurane or 1085 ml of vapour at 25 °C. From the area above the curve, we calculated the uptake of isoflurane by the SG as 5.0 ml of liquid isoflurane which compares well with the observed gain in weight. In the second experiment the weight gain was 7.4 g, equivalent to 5.0 ml liquid isoflurane (1000 ml vapour), with the area above the curve indicating an uptake of 4.23 ml.

The isoflurane was recovered from the SG by flushing with warm (60 °C) humidified air until the colour change indicated full hydration. The outflow was dried over anhydrous calcium chloride and any isoflurane in the gas flow was condensed by passage into a glass tube immersed in chippings of solid carbon dioxide (Cardice). The liquid that condensed was identified as

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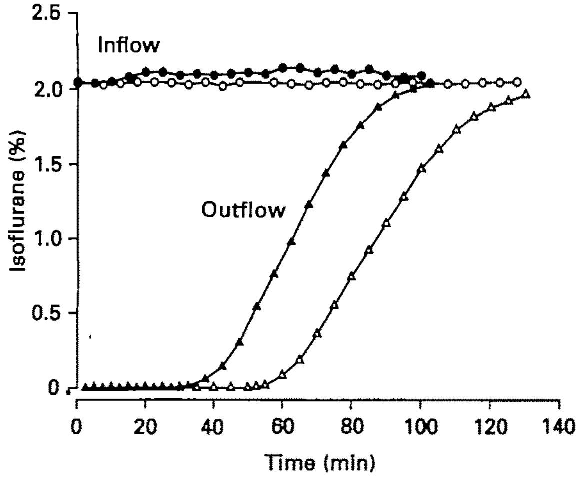

FIG. 1. Inflow and outflow isoflurane concentrations for dry silica gel. Open symbols = nitrogen flow 550 ml min^{-1}; closed symbols = nitrogen flow 620 ml min^{-1}.

isoflurane by gas chromatography and its characteristic odour. The volume collected represented recoveries of 96% and 92%.

The experiment was repeated using SG fully saturated with water and a flow of nitrogen 550 ml min^{-1}, also fully saturated at ambient temperature by a hot water humidifier. Isoflurane 2% was added to the nitrogen and allowed to flush the humidifier before being diverted through the wet SG. Outflow samples were taken every 1 min for 5 min, and the inflow sampled as before. Within 1 min, outflow concentration was 83% of the inflow, and by 4 min there was no detectable difference between inflow and outflow samples. Considering the washout of the air initially in the SG container, this represents negligible absorption of isoflurane.

COMMENT

We have shown that dry SG may absorb approximately 31 times its own volume of gaseous isoflurane, which can be recovered almost totally by displacement from the SG with a more polar compound such as water. The absorption of isoflurane is (predictably) abolished completely by hydration of the SG. These findings are not unexpected, as SG is known to absorb many organic compounds, including ethers [1], and halogenated hydrocarbons [2]. Absorption of halothane has been described previously, and SG has been used to collect atmospheric halothane over several hours to assess exposure of theatre personnel [3]. The cost of SG (£5.60 per 500 g) makes it unlikely to be of practical use for anaesthetic scavenging.

For research purposes, the absorption of isoflurane by SG may be beneficial or detrimental, depending on the circumstances. For helium analysis in our system the removal of isoflurane prevents its interference with the katherometer readings, but also alters the apparent helium concentration in the spirometer by an amount corresponding to the concentration of the anaesthetic. Care must be taken, therefore, when using SG in research involving modern volatile anaesthetic agents, and it may be appropriate to use calcium chloride as an alternative.

This study has not attempted to elucidate the mechanism of isoflurane uptake by SG, or the effect of factors such as mesh size, container shape or isoflurane concentration on our observations. We have simply demonstrated the general phenomenon, and how it affects gas analysis under the individual circumstances of our research.

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PROPOFOL SEDATION FOR OUTPATIENT UPPER GASTROINTESTINAL ENDOSCOPY: COMPARISON WITH MIDAZOLAM

K. W. PATTERSON, P. B. CASEY, J. P. MURRAY, C. A. O'BOYLE AND A. J. CUNNINGHAM

SUMMARY

The objectives of this study were to assess midazolam and propofol as sedative agents for outpatient gastrointestinal endoscopy, with particular reference to recovery profile, amnesic effects, and haemodynamic state and oxygenation during the procedure. Forty consecutive patients were allocated randomly to two groups. Patients in group I ($n = 19$) *received midazolam 81 (SEM 32)* $\mu g\ kg^{-1}$*; those in group II* ($n = 21$) *received propofol 950 (400)* $\mu g\ kg^{-1}$*. Both agents were administered as single injections to similar end-points of sedation. Psychomotor function was assessed using the digit symbol substitution test (DSST). Amnesia was measured with a visual memory test and subjective questionnaire. Patients in group I had a lower DSST score than those in group II* ($P < 0.01$)*, indicating a hangover effect from midazolam. Amnesia was similar in the two groups up to the time of removal of the endoscope. More patients in group II remembered removal of the endoscope* ($P < 0.001$)*. Oxygen desaturation from baseline was similar in both groups* ($P < 0.01$)*. An increase in heart rate and decrease in mean arterial pressure were noted in both groups. Propofol provided more rapid recovery compared with midazolam, but was associated with pain on injection, a short amnesia span, and reduced patient acceptance.*

KEY WORDS
Anaesthetics, intravenous. propofol. Gastrointestinal tract. endoscopy. Recovery. measurement. Hypnotics midazolam.

Outpatient endoscopy requires reliable sedation of short duration and devoid of side effects. The i.v. use of benzodiazepines is a popular technique. Midazolam is chosen frequently because of its short elimination half-life, lack of active metabolites and potent amnesic properties [1, 2]. Propofol (2,6,diisopropylphenol), a sterically hindered phenol, has a rapid onset, large volume of distribution, lack of active metabolites and short elimination half-life; these properties suggest that it may be suitable for outpatient gastrointestinal endoscopy.

The objectives of the study were to compare midazolam and propofol as sedative agents for outpatient endoscopy, with particular reference to recovery profile, amnesic effects and cardiorespiratory changes.

METHODS AND RESULTS

Following institutional Ethics Committee approval and informed consent, we studied 40 patients (ASA I–II) undergoing elective outpatient gastrointestinal endoscopy; they were allocated randomly to receive midazolam (group I) or propofol (group II). Patients receiving psychotropic medication or drugs known to interact with benzodiazepines or propofol were excluded. After topical anaesthesia of the oropharynx with 120 mg lignocaine, each agent was administered as a single injection to the same end-points of sedation (dysarthria, nystagmus or ptosis). The same physician, who was not blinded to the agent, administered all drugs. As the onset time for propofol is approximately one arm–brain

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circulation time, whereas that for midazolam is about 2 min, a separate injection scheme was adopted in each group. Midazolam was diluted to a concentration of 0.5 mg ml^{-1} and injected at a rate of 1 ml every 15 s until the patient demonstrated signs of sedation; propofol was injected undiluted at a rate of 1 ml every 5 s to the same end-points. In an effort to avoid pain on injection, lignocaine 1 ml was added to the propofol immediately before injection.

All patients breathed room air throughout the procedure. Monitoring included oxygen saturation, automatic arterial pressure and ECG. Cardiorespiratory data were recorded at the following times: baseline, i.v. cannulation, topical anaesthesia of the oropharynx, administration of drug, insertion of mouth gag, insertion of endoscope, biopsy, removal of endoscope and 5 min after endoscopy.

Endoscopies were carried out by the same endoscopist using an Olympus endoscope and blinded to the drug administered. Gastric or oesophageal biopsies were taken from all patients.

The study was blind to the investigator assessing the patients.

Psychomotor function using the digit symbol substitution test (DSST), administered in the standard manner, was assessed before endoscopy and at 30 and 90 min after administration of drug. This test has been found previously to be sensitive to the effects of benzodiazepines and to be appropriate for outpatient use [3].

The degree of amnesia was measured with a visual memory test and a subjective questionnaire [3]. Questions regarding complications and patient satisfaction with the sedation were included also.

Statistical methods included analysis of variance (ANOVA), the Mann–Whitney *U* test, Fisher's Exact Probability test, Wilcoxon Matched Pairs test, and the chi-square test. $P < 0.05$ was considered significant. Data are expressed as mean (SEM), unless stated otherwise.

The two patient groups were similar with regard to age, weight, sex distribution and duration of procedure; 63 % of patients in group I and 52 % of patients in group II were having repeat endoscopy. Mean doses of midazolam and propofol to achieve sedation were 81 (32) μg kg^{-1} and 950 (400) μg kg^{-1} in groups I and II, respectively. All patients remained conscious during endoscopy.

The change in DSST score from before endoscopy to 30 and 90 min after injection is illustrated in figure 1. Deterioration in psychomotor function at 30 min was noted in group I (midazolam) ($P < 0.01$). Group II patients (propofol) show no change from baseline. At 90 min, psychomotor function had returned to baseline values in both groups.

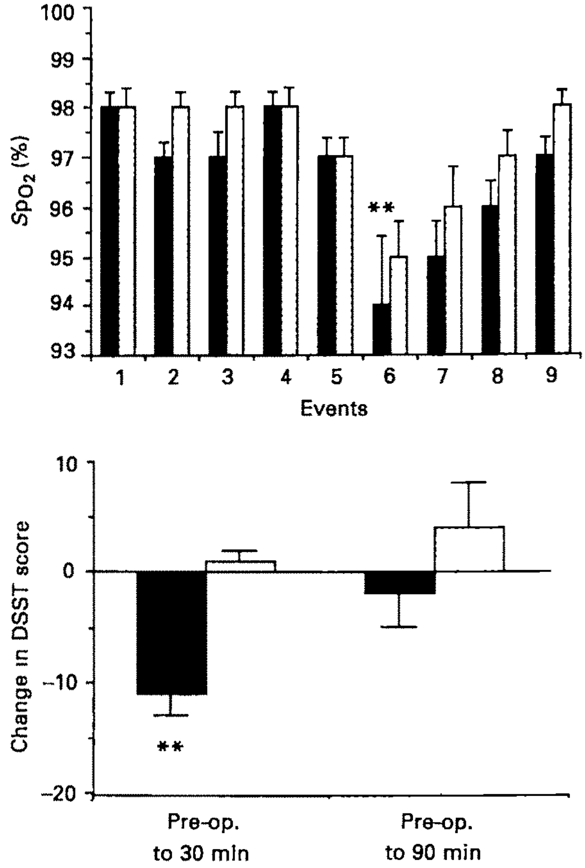

FIG. 1. Oxygen saturation data (mean, SEM) and change in DSST score from before operation (Pre-op) to 30 and 90 min after injection of propofol and midazolam (mean, SEM). Events. 1 = Baseline; 2 = i.v. cannulation; 3 = topical anaesthesia of the oropharynx; 4 = administration of drug; 5 = insertion of mouth gag; 6 = insertion of endoscope; 7 = biopsy; 8 = removal of endoscope; 9 = 5 min after endoscopy. $^{**}P < 0.01$.

Both drugs showed similar amnesic properties up to the time of removal of the endoscope. However, 68 % of group I patients were amnesic for this event, compared with 14 % of group II patients ($P < 0.001$). Early amnesic effects were similar in the two groups; however, 74 % of patients in group I were amnesic for the third photograph shown immediately after removal of the endoscope, compared with 38 % of patients in group II ($P < 0.05$).

The main complication was pain on injection: 29% of patients in group II experienced moderate to severe pain, compared with 5% in group I ($P < 0.05$). Twenty-four percent of patients in group II indicated that they would prefer another method of sedation during future endoscopy, compared with 5% in group I ($P < 0.05$). All the patients who expressed dissatisfaction with the procedure had experienced pain on injection. Other complications were similar in the two groups.

Oxygen saturation decreased in both groups after administration of drug ($P < 0.01$). There was no difference between the groups (fig. 1).

Heart rate increased in both groups during the procedure, but was less in the propofol group at insertion of the mouth gag ($P < 0.05$) and 5 min after endoscopy ($P < 0.05$). Both drugs caused a reduction in mean arterial pressure following administration of drug, but baseline mean arterial pressure was less in group II ($P < 0.05$).

COMMENT

Propofol and midazolam produced satisfactory sedation and acceptable amnesia during upper gastrointestinal endoscopy. Both drugs produced similar arterial desaturation. The decrease in saturation as a mean value was not clinically important (from 98% to 94%). However, when one considers that oxygen saturation decreased to 90% or less in 26% of patients in group I and 19% of patients in group II, its clinical importance becomes apparent. In the presence of pre-existing cardiac disease, hypoxaemia of this magnitude could predispose to cardiac arrhythmias.

Propofol-treated patients had a greater DSST score 30 min after endoscopy, indicating more rapid recovery than those in the midazolam group and implying that the use of propofol may allow earlier discharge. However, to demonstrate improved "street fitness" after use of propofol, more elaborate recovery tests would be needed.

More patients in the propofol group indicated that they would prefer an alternative method of sedation if future endoscopy was necessary. This may reflect the fact that 29% of patients in group II experienced moderate to severe pain on injection, compared with 5% in group I. The addition of 1% lignocaine 1 ml to the propofol before administration of drug failed to eliminate pain on injection.

There is a wide dose variation reported in the literature when midazolam is used for sedation (50–110 $\mu g\ kg^{-1}$) [1]. The mean dose in our study (81 (32) $\mu g\ kg^{-1}$) was comparable to the doses used by other workers. The mean dose of propofol was 950 (400) $\mu g\ kg^{-1}$, which is considerably smaller than that reported previously for sedation. Gepts and colleagues used propofol 2 $mg\ kg^{-1}$ followed by an infusion as a sedative technique for colonoscopy [4] and Dubois and colleagues used 1.76 $mg\ kg^{-1}$ followed by an infusion for sedation during gastrointestinal endoscopy [5]. These doses are in the range used for induction of anaesthesia. No control groups were included in these studies, presumably because it is difficult to compare fixed doses of agents with differing onset times. We overcame this problem by titrating both drugs to the same clinical end-points of sedation using an injection technique which allowed for the variation in onset time.

Our study confirms the amnesic effects of both drugs [1, 4]. Amnesia for the total procedure may be important in that it improves patient acceptance of a repeat endoscopy. To increase duration of amnesia in group II it would probably be necessary to give patients an infusion of propofol. It is worth noting that the long duration of amnesia associated with midazolam may delay early discharge from a day-case unit and be hazardous in unsupervised patients.

Patients in the propofol group had a significantly slower heart rate than those in the midazolam group, and this persisted in spite of a decreased mean arterial pressure. This effect of propofol has been demonstrated previously and may be of benefit in patients as it reduces myocardial oxygen demand [6]. However, a reduction in mean arterial pressure and its effect in reducing myocardial blood supply may offset any benefits gained by a reduced heart rate.

In conclusion, both agents are suitable for sedation during gastrointestinal endoscopy. Propofol may offer some advantages in a day-case setting, with its rapid recovery profile and limited amnesic effects. However, its disadvantages include pain on injection, a short amnesia span when administered by single injection and reduced patient acceptance compared with midazolam. We recommend that supplementary oxygen be administered to all patients undergoing endoscopy when either propofol or midazolam is used for sedation. Monitoring should include ECG, arterial pressure and oxygen saturation. It is the practice in many endoscopy units for the endoscopist to administer the sedative and then carry out the procedure with a nurse assistant. In view of our findings, we strongly recommend that a second doctor, other than the endoscopist, administer the sedation and remain with the patient for the duration of the procedure.

ACKNOWLEDGEMENT

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EXTRADURAL HAEMATOMA AFTER CONTINUOUS EXTRADURAL ANAESTHESIA

I. H. TEKKOK, O. CATALTEPE, K. TAHTA AND V. BERTAN

SUMMARY

We report a case of extradural haematoma occurring after extradural anaesthesia in an anticoagulated patient. The diagnosis was confirmed by magnetic resonance imaging and the haematoma was evacuated surgically. A search of the literature revealed only five previous reports of extradural haematoma in association with extradural anaesthesia.

KEY WORDS

Anaesthetic techniques. extradural Complications: extradural haematoma.

Extradural haematoma (EH) is an uncommon, but treatable cause of spinal cord compression. Since the original description by Jackson in 1869 [1], more than 200 cases of varying aetiology have been reported [2]. Trauma, anticoagulation, bleeding diatheses and intraspinal vascular malformations have been associated with EH, but occasionally it may occur without any apparent cause [2]. In recent years, more than 30% of reported cases have been associated with anticoagulant therapy [3]. Iatrogenic EH, although rare, may occur as a complication of lumbar puncture or extradural spinal anaesthesia [4]. We present a case of EH that occurred after continuous extradural anaesthesia while the patient was receiving anticoagulant therapy, and discuss the aetiology, diagnosis and treatment of this unusual complication.

CASE REPORT

A 42-year-old man, with a history of diabetes mellitus and chronic pancreatitis of 4 years duration, developed left-sided intermittent claudication about 1 month before his admission to another hospital. Reduced pulsation of the left-sided dorsal pedal and posterior tibial arteries was noted. A digital subtraction angiogram showed left external iliac artery obliteration. An iliofemoral bypass graft was performed under extradural anaesthesia. The extradural space was entered with a single puncture at the L2–3 interspace with a 90-mm 17-gauge Tuohy needle. A 90-cm, 19-gauge flexible catheter with stilette introducer and open distal end (Vygon) was passed about 2–3 cm beyond the tip of the needle. Fifteen millilitre of 2% lignocaine was injected through the catheter. The procedure was uncomplicated and no haemorrhage was noted.

One hour after the start of surgery, the first dose of heparin 5000 u was given i.v. The extradural catheter was left *in situ* for the next 2 days for provision of pain relief and sympathetic block by the intermittent injection of 2% lignocaine. Meanwhile, heparin 5000 u twice daily and dextran 40 solution 1000 ml daily were given. During this period all pulses were present and full power and sensation were noted in the legs. The extradural catheter was removed approximately 48 h after insertion. Three hours later, the patient complained of paraesthesia and numbness of his feet which progressed to complete paraplegia within 12 h. An Iohexol-enhanced CT scan of the spine was performed, but surgery was not considered, under the impression that the scan was normal. No further heparin was administered.

Fourteen days after the onset of paraplegia the patient was brought to our centre by his relatives. On neurological examination, anaesthesia below T9 and total paraplegia were observed with no anal tone or reflex. A magnetic resonance (MR)

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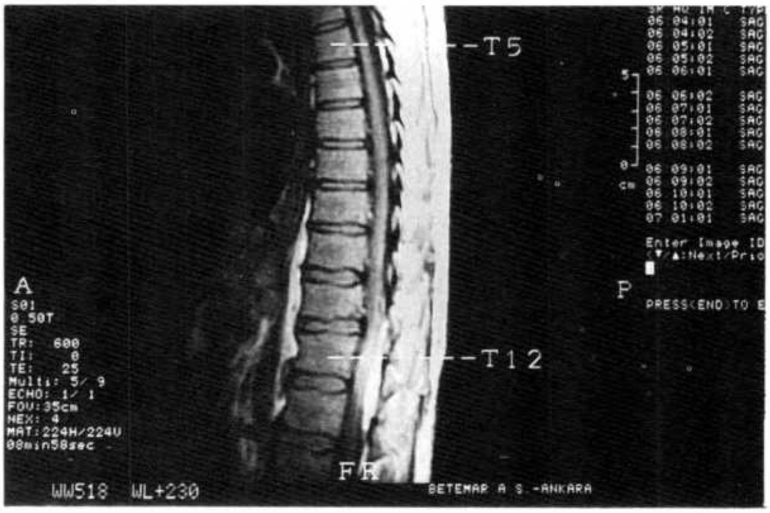

FIG. 1. Sagittal MR view (GE 0.5 T, TR 600/TE 25). A fusiform hyperintense lesion is present behind the cord.

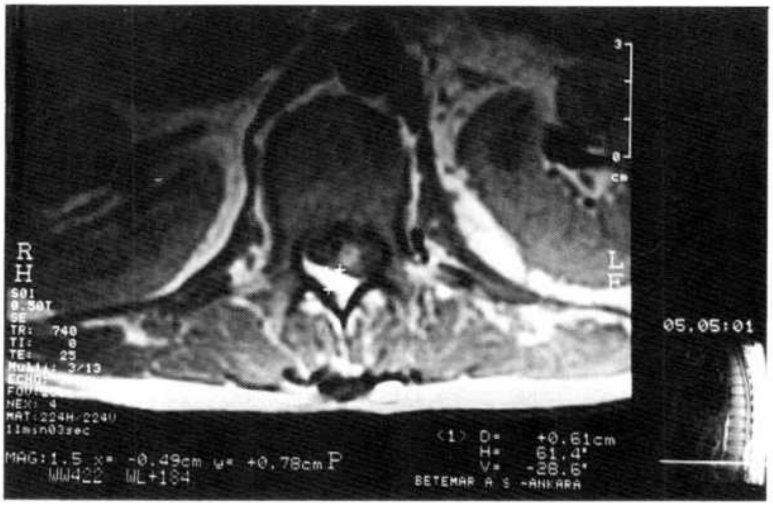

FIG. 2. Axial MR view (TR 740/TE 25). Hyperintense lesion 0.61 cm thick displaces the spinal cord anteriorly and to the left.

scan was performed and showed a posteriorly placed, "cigarette shaped" [5] haematoma extending from T12 to L1 on both T1- (fig. 1), proton density- and T2-weighted images. The lesion was displacing the spinal cord anteriorly and to the left (fig. 2). Although late, a decompressive laminectomy was considered to give a chance of recovery to the patient. Prothrombin, activated partial thromboplastin, clotting and bleeding times and platelet counts were found to be within normal limits.

A partial (inferior) T11 and total T12 and L1 laminectomy was performed. A 2 × 1 × 5-cm right-sided posterolateral extradural haematoma was found and removed. Histopathological examination revealed an organizing haematoma.

Upon discharge to a foreign rehabilitation centre, the patient demonstrated no major improvement in lower extremity function or sensation, but was mobile with the help of braces, facilitated by the spasticity that developed 1 month after operation.

DISCUSSION

Although blood dyscrasias and anticoagulation therapy are recorded as contraindications to extradural or subarachnoid anaesthesia in most textbooks, there have been a few reports of extradural haematoma in patients given anticoagulants after catheter placement [6–10], mostly with poor outcome because of late diagnosis and late treatment. The incidence of EH after extradural anaesthesia may be greater, as such a complication is not always reported.

The extradural space contains loose areolar tissue and a dense network of large, thin-walled and valveless veins. When these veins are torn by a needle or catheter, a small amount of bleeding occurs into the extradural space. If haemostatic mechanisms are normal, the defect will be sealed, but if the patient's coagulation mechanisms are impaired, haemorrhage may continue or be restarted if the clot is dislodged by the withdrawal of the catheter.

The typical presentation of EH is acute back and radicular pain leading to paresis which may then progress to para- or tetraplegia over a variable time. We have found only one other report of "painless" EH as occurred in our patient [11].

Recovery from EH depends largely on the extent and duration of spinal cord compression and early recognition is mandatory. A high index of suspicion is necessary for early diagnosis, when detailed and frequent neurological examinations should be performed from the time of catheter insertion until 24 h after the catheter removal. Prolonged numbness or weakness, paraesthesia and severe back pain should prompt neurosurgical evaluation.

Conventional myelography may be useful in the diagnosis, but it requires insertion of a needle, which may be regarded as a relative contraindication to its use. It should be considered only after coagulation parameters return to normal and if alternative tests are not available. Myelography will show an extradural mass, but cannot differentiate between blood, pus or tumour. CT scanning may be useful but it, too, has disadvantages. First, it cannot survey satisfactorily all the spinal canal; second, resolution may be poor within the thoracic spinal canal compared with the lumbar or cervical regions. Typically, an EH would appear as a hyperdense, biconvex mass adjacent to the bony canal. Deliniation of an EH may be improved by CT–myelography, when characteristic extradural lenticular collections may be seen on either side of the midline [12].

Magnetic resonance imaging does not require either a lumbar puncture or ionizing radiation and is the preferred diagnostic technique for spinal imaging. On MR scans, an acute EH appears as iso- or minimally hyperintense on T1 and heterogeneously hyperintense on T2 images [5, 13]. Subacute EH show hyperintensity on both T1- and T2-weighted images which can be attributed to the paramagnetic effect of intracellular methaemoglobin with subsequent cell lysis and resultant free haemoglobin [14].

Although it has been emphasized that only emergency or early surgery of EH produces good results [15], there have been reports of occasional patients with spontaneous remission [3]. Notably, Shima, Mihara and Hachisuga reported a patient recovering completely after surgery 18 days after the onset of symptoms [16]. Percutaneous needle aspiration has been suggested as an alternative treatment [3]; nevertheless, EH almost always produces a permanent neurological deficit unless there is prompt surgical intervention.

We conclude that extradural anaesthesia remains contraindicated in the presence of impaired coagulation. If it is undertaken in these circumstances a high degree of clinical suspicion of EH should be maintained, with frequent neurological examinations from insertion of the catheter to 24 h after its removal. Early recourse to appropriate investigations and surgery is mandatory for successful management.

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NON-CARDIOGENIC PULMONARY OEDEMA AFTER TRANSFUSION WITH GRANULOCYTE ANTIBODY CONTAINING BLOOD: TREATMENT WITH EXTRACORPOREAL MEMBRANE OXYGENATION

M. H. WORSLEY, C. J. SINCLAIR, C. CAMPANELLA, D. C. KILPATRICK AND P. L. YAP

SUMMARY

A 45-yr-old man developed severe non-cardiogenic pulmonary oedema after a blood transfusion reaction which was resistant to standard therapy. We describe its successful treatment with extracorporeal membrane oxygenation.

KEY WORDS

Complications. non-cardiogenic pulmonary oedema Surgery · cardiac, ECMO. Transfusion stored blood

Extracorporeal membrane oxygenation (ECMO) may be suitable for treatment of severe, but self limiting, disorders of pulmonary gas exchange, but it has failed to find firm indications in adults. We describe its use in treatment of non-cardiogenic pulmonary oedema following transfusion with blood containing an antigranulocyte antibody.

CASE REPORT

A 45-yr-old, 80-kg water bailiff and gamekeeper with an 8-month history of disabling angina presented for coronary artery surgery. His past medical history was unremarkable, with no previous operations and no history of allergy. He did not smoke and was a reformed drinker. Current medication comprised atenolol 50 mg day^{-1} and aspirin 300 mg day^{-1}, which controlled his symptoms well. Physical and laboratory examinations were normal. Angiography showed good left ventricular function with antero-apical hypokinesia and an ejection fraction of 68%, an occluded right coronary artery, and severe stenoses in the left anterior descending and circumflex arteries. In view of his age, extent of disease and desire for an active lifestyle, it was decided to proceed with surgery.

After premedication with oral nitrazepam and atenolol the evening before surgery and lorazepam, transdermal glyceryl trinitrate and i.m. papaveretum and atropine in the morning, anaesthesia was induced and maintained with midazolam, alfentanil and pancuronium. Nitrous oxide was used until aortic cannulation, after which the lungs were ventilated with oxygen-enriched air. Monitoring was facilitated with radial arterial and internal jugular venous cannulae.

The chest was opened via a midline sternotomy and, after full heparinization and cannulation, cardiopulmonary bypass was established and the patient cooled to 28 °C. Saphenous vein was grafted to the first obtuse marginal and posterior descending branches, and the left internal mammary artery was grafted to the left anterior descending coronary artery. Bypass time was 97 min and cross-clamp time was 62 min. After rewarming, the patient was weaned easily in sinus rhythm without inotropic support and treated with an infusion of glyceryl trinitrate 10 μg min^{-1}, producing a systemic arterial pressure of 105/

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65 mm Hg, heart rate 75 beat min^{-1} and central venous pressure (CVP) +7 mm Hg; Pa_{O_2} was 57 kPa and Pa_{CO_2} 4.9 kPa, with FI_{O_2} 1.0 and minute volume 9.5 litre min^{-1}.

Thirty minutes after bypass, protamine 600 mg had been given, the blood from the pump restored to the patient, one unit of whole blood administered, and an infusion of gelatin solution was in progress. The patient was stable, with unchanged haemodynamic variables.

After a further 15 min, arterial pressure decreased to 95/50 mm Hg, CVP increased to +12 mm Hg and heart rate was 85 beat min^{-1}. These changes were followed closely by the appearance of frank pulmonary oedema from the tracheal tube, accompanied by an increase in peak airway pressure from 11 to 36 cm H_2O. Arterial blood-gas analysis with a minute volume of 9.5 litre and FI_{O_2} 0.5 showed Pa_{O_2} 7.3 kPa and Pa_{CO_2} 6.3 kPa. Treatment was commenced with adrenaline, infusion of dopamine, chlorpheniramine, frusemide, aminophylline and methylprednisolone. Minute ventilation was increased, positive end expiratory pressure (PEEP) applied, and FI_{O_2} increased to 1.0. Further investigation with flow directed pulmonary artery (PA) catheterization via the right atrium revealed PA pressures of 38/20 mm Hg and wedge pressure 10 mm Hg.

The course over the next 3 h was stormy, with systemic hypotension (70/40 mm Hg), pulmonary hypertension (38/22 mm Hg) and tachycardia (115 beat min^{-1}) despite filling pressures in both atria of about 12–13 mm Hg, with worsening pulmonary oedema. Cardiovascular function was supported with infusions of noradrenaline 0.08 μg $\text{kg}^{-1}\,\text{min}^{-1}$ and dopamine 2 μg $\text{kg}^{-1}\,\text{min}^{-1}$. Cardiac output at this stage was 4.5–5 litre min^{-1}, giving calculated SVR and PVR of 590 and 214 dyn s cm^{-5}, respectively.

At this stage, despite increasing minute ventilation to 14 litre min^{-1}, resulting in increased airway pressures (40 cm H_2O), and with PEEP of 4 cm H_2O, pulmonary oedema persisted with deteriorating gas exchange. It was thought unwise to increase ventilation further as this might threaten the integrity of the internal mammary graft.

In view of the severe non-cardiogenic pulmonary oedema, it was decided to institute ECMO. This was established after re-heparinization, initially from femoral vein to femoral artery, with a Sci Med 3500 membrane oxygenator with roller pump and reservoir at a flow of 2.5 litre min^{-1}. Activated clotting times were maintained between 300 and 350 s. This produced a marked improvement in gas exchange with Pa_{O_2} 30 kPa and Pa_{CO_2} 4 kPa. Unfortunately, the circulation in the leg became compromised with this arrangement and in view of the patient's active occupation and lifestyle, ECMO was instituted between right atrium and ascending aorta. Satisfactory gas exchange was again established and the circulation to the leg restored.

The patient was returned to the intensive care unit 7 h after bypass with the ECMO system *in situ* through an open median sternotomy. ECMO was maintained throughout the first night after operation with flows of 2.5 litre min^{-1}. The lungs were ventilated with FI_{O_2} 0.6 at a minute volume of 10 litre min^{-1} and PEEP of 5 cm H_2O. Cardiovascular support was continued with infusions of dopamine and noradrenaline. Because of heparinization, bleeding was considerable, requiring packs to be changed several times. Total blood loss while on ECMO was at least 5 litre; this was replaced with whole blood, platelets and plasma protein solution. Sedation during this period was maintained with papaveretum and midazolam, and neuromuscular block maintained with pancuronium.

Pulmonary function improved during the first day after operation, and the patient was eventually weaned from ECMO 20 h after bypass, allowing the chest to be closed and coagulation abnormalities to be corrected. Over the following 24 h ventilatory and inotropic support were decreased, the chest x-ray improved, and the trachea was extubated on the second day after operation. Pa_{O_2} 9.5 kPa while the patient breathed air was recorded at this time. He was discharged from the intensive care unit on the third day, and from the cardiac unit on the ninth day. Pulmonary function tests at this stage showed a marked restrictive deficit, but the patient has since returned successfully to his active occupation.

Subsequent investigation revealed a strongly positive anti-granulocyte cross match with the serum from the unit of whole blood administered in the period immediately after bypass. Antilymphocyte matches were negative, and immunoglobulin (including IgE) and complement concentrations were unremarkable. It seems likely, therefore, that the patient's complication was caused by an anti-neutrophil antibody present in the unit of whole blood administered after termination of bypass. This accords with an onset time of between 30 min and 2 h. The donor of the implicated unit was traced, and was found to be a 41-year-old woman with no history of blood transfusion but a complicated obstetric history. Her first pregnancy was uncomplicated and resulted in the birth of a normal boy, but her subsequent three pregnancies resulted in a neonatal death, followed by two early second trimester missed abortions.

DISCUSSION

Fulminant non-cardiogenic pulmonary oedema is a rare but potentially lethal complication of cardiopulmonary bypass. Several causes have been postulated, including endotoxin, protamine, complement activation by pump or oxygenator and, as in this patient, transfusion reaction [1, 2]. White blood cell antibodies or leucoagglutinins have been implicated in both experimental models and a few clinical cases. In these patients white blood cell antibodies have most commonly been found in donor plasma, but occasionally in recipients [3]. Following reaction between antibody and white blood cell there is release of various toxins, including oxygen species, proteolytic enzymes and activated complement. When antibodies are found in donor sera, these are often from multiparous women, arising presumably from sensitization to fetal alloantigens during pregnancy. Potential reactions cannot be detected by conventional cross matching.

The frequency of reaction following passive transfer of leucocyte antibody is estimated at 0.02% of all transfusions, but may be commoner than is widely appreciated. Leucoagglutinating or lymphocytotoxic antibodies have been shown consistently to be present in around 17% of pregnant women and to persist for 3 yr thereafter in 55%. Antibodies have been shown to be present in approximately 3% of previously transfused male donors. These groups at risk of having such antibodies represent perhaps 1.5% of the blood donor population [4]. Donations with leucocyte antibodies are dangerous only for patients with the specific leucocyte antigens which would react with them. This is an extremely rare circumstance. If donations are found to have leucocyte antibodies, they may still be used to produce washed red blood cells. Red blood cell concentrates may contain sufficient remaining plasma, and therefore antibody, to cause pulmonary reactions.

Management of non-cardiogenic pulmonary oedema includes prompt recognition. Suspicion is warranted in situations in which there is particular risk such as blood transfusion or cardiac surgery. Indeed, prophylaxis with antihistamine and steroid has been recommended before cardiopulmonary bypass [2]. Appropriate resuscitative measures should include respiratory support with oxygen, bronchodilators, tracheo-bronchial toilet, positive pressure ventilation and PEEP if required. Significant effusions should be drained. The circulation should be monitored with central venous, pulmonary artery or, if possible, left atrial catheterization, filling pressures optimized, and inotropic support given in severe cases. Metabolic derangements must be treated. Specific measures include antihistamines such as chlorpheniramine, pharmacological doses of steroid to minimize pulmonary endothelial damage, and adrenaline to antagonize the effects of histamine and for its bronchodilating, inotropic and vasoactive actions.

Because of its cost in terms of labour, expense and complications, the use of ECMO has so far been limited. It has failed to improve mortality in severe acute respiratory failure, although recent techniques which emphasize elimination of carbon dioxide may be more promising [5]. Indications outside the field of neonatal medicine are not defined [6, 7]. It would appear to be appropriate for the treatment of a short, self limiting illness with a rapidly reversible lung lesion during which support could be applied for as short a period as possible to minimize problems of complications and resources. A recent example is its successful use in the sickle cell syndrome [8].

Non-cardiogenic pulmonary oedema after cardiopulmonary bypass or blood transfusion would seem to be such a situation in which the nature of the lung lesion is severe but transient, and ECMO may be appropriate in the most severe cases in which oxygenation is inadequate, despite medical treatment. In the patient we describe, acceptable gas exchange was achieved with modest flows for the 16-h period before the worst of the pulmonary effects diminished. The major complications encountered were lower limb ischaemia distal to the cannulation site, and bleeding from heparinization. The former could perhaps have been modified by the use of smaller cannulae and therefore slower flow rates, but obviously a balance must be found between cannula size and a flow rate sufficient to maintain oxygen delivery. We chose to use activated clotting times in the range 300–350 s, which have been suggested for use with our system [9]. It may be possible to minimize bleeding using heparin-bonded extracorporeal systems and lesser degrees of systemic heparinization with careful monitoring of transmembrane pressure [10].

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A SYSTEM FOR AUTOMATIC FEEDBACK CONTROL OF PLASMA POTASSIUM CONCENTRATION

M. P. D. HEINING, R. K. DEBEY, S. W. MCJAMES, W. S. JORDAN AND D. R. WESTENSKOW

SUMMARY

A system is described for automatic feedback control of plasma potassium concentration in experimental animals. Plasma potassium was monitored continuously and the signal compared with the desired plasma potassium concentration. The resulting error signal controlled the infusion rates of a concentrated potassium chloride solution (50 or 200 mmol litre^{-1}) and a solution of 50% glucose with insulin 200 u litre^{-1}. Plasma potassium was increased or decreased to the desired concentration at various rates, dictated by the controller constants. Increases were achieved significantly faster than reductions. The system may prove useful for elucidating the fate of infused potassium and for determining the optimum rate of insulin infusion in hyperkalaemia. If adapted for clinical use, it may find applications in the management of various abnormalities of potassium homeostasis.

KEY WORDS

Computers: closed-loop control. Ions: potassium. Monitoring: intra-arterial.

Abnormalities of plasma potassium concentration ([K$^+$]) are a common problem in patients undergoing major surgery and in those requiring intensive care. Treatment is empirical, depending on frequent blood sampling to follow the response to therapy. Even with the rapid results available from potassium ion-selective electrodes, correction of abnormalities and maintenance of a stable plasma [K$^+$] may be difficult.

Automatic feedback control may provide a system for rapid, safe correction of plasma [K$^+$]. This paper describes such a system, and its use in experimental animals.

MATERIALS AND METHODS

Continuous monitoring of plasma potassium

Plasma potassium was monitored continuously in the femoral artery by means of a 1-mm o.d. valinomycin-based catheter-tip ion-selective electrode (fig. 1) [1] inserted into the femoral artery. The internal reference electrode was a silver–silver chloride electrode and the internal filling solution was potassium chloride 100 mmol litre^{-1}. The external reference electrode was a silver–silver chloride electrode contained in the barrel of a 1-ml syringe which was plugged into a saline-filled catheter in the femoral vein on the same side. This system has been shown to give reliable recordings which are relatively free from interference, and also has a response time of less than 1 s [2]. All electrodes used had a response of at least 95% of that predicted by the Nernst equation.

The electrode output was fed to an amplifier and subsequently passed through a simple RC filter with a cut-off frequency of 0.27 Hz. This signal was sampled at 10-s intervals using a 12-bit a/d convertor in the computer. Additional filtering was performed digitally by averaging the present sample with the previous average.

The electrode was calibrated by immersion in aqueous standard solutions before use, to yield the electrode response slope, and a one-point cali-

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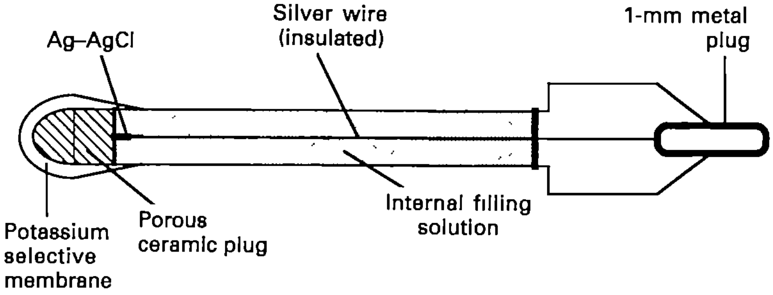


FIG. 1. Arrangement of the components of the ion-selective catheter electrode.

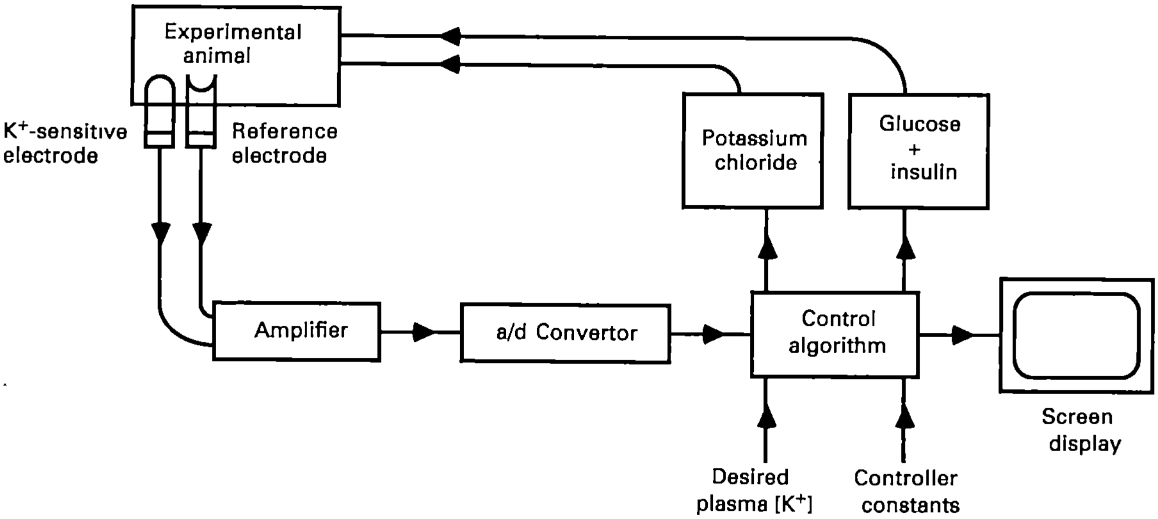
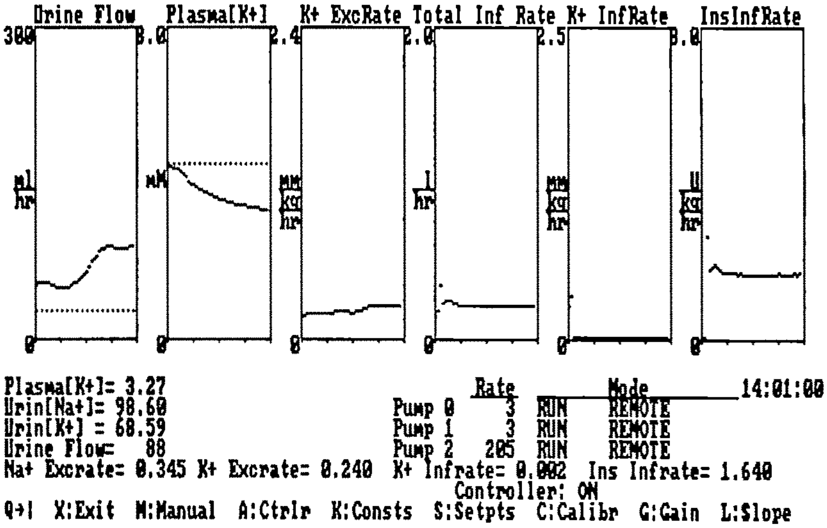


FIG. 2. Arrangement of the feedback loop for automatic control of plasma concentration of potassium ([K⁺]).

bration was performed after insertion into the circulation, to yield the electrode offset. The calibration sample was taken from the other femoral artery and [K⁺] measured using a Nova 1 Na/K electrode. Any electrode drift was corrected by repeating the one-point calibration every 30 min. Recalibration was performed if the plasma [K⁺] measured with the Nova electrode differed by more than 0.2 mmol litre^{-1} from that measured by the indwelling electrode. Usually, the animal was heparinized, to prevent clot formation on the electrode tip.

Control algorithm and infusion system

The control algorithm was written in BASIC on an IBM personal computer, and used a conventional proportional–integral–differential system with separate control equations for the potassium chloride infusion and the glucose–insulin infusion. The control system was arranged so that one infusion declined to zero when the other infusion started, so that both infusions were not running simultaneously. The set-point of plasma [K⁺] and the controller constants were changed at any time. The output from the control program drove two specially adapted infusion pumps (IVAC Inc.) which were fed into a peripheral vein. One of these contained a concentrated solution of potassium chloride (50 mmol litre^{-1} or 200 mmol litre^{-1}) and the other contained 50 % glucose with insulin 200 u litre^{-1}. The maximum rate of infusion of potassium chloride was 2.5 mmol kg^{-1} h^{-1}, and the maximum rate of infusion of the glucose–insulin solution was insulin 5 u kg^{-1} h^{-1}. Plasma [K⁺] was measured every 10 s and infusion rates were adjusted every 1 min. The arrangement of the feedback loop is summarized in figure 2.



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Plasma[K+]= 3.27                                     Rate          Mode          14:01:00
Urin[Na+]= 98.60                             Pump 0     3   RUN    REMOTE
Urin[K+] = 68.59                             Pump 1     3   RUN    REMOTE
Urine Flow=   88                             Pump 2   205   RUN    REMOTE
Na+ Excrate= 0.345 K+ Excrate= 0.240  K+ Infrate= 0.002  Ins Infrate= 1.640
                                                Controller: ON
Q+|  X:Exit  M:Manual  A:Ctrlr  K:Consts  S:Setpts  C:Calibr  G:Gain  L:Slope
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FIG. 3. Representation of screen display during control system use.

The program also produced a screen display (fig. 3). This was updated every 1 min to display the changes over the previous 40 min in plasma [K$^+$] (mmol litre^{-1}), total i.v. infusion rate (litre h^{-1}), potassium infusion rate (mmol kg^{-1} h^{-1}), insulin infusion rate (u kg^{-1} h^{-1}), urine flow (ml h^{-1}) and potassium excretion rate (mmol kg^{-1} h^{-1}). The last two were obtained from a Vitalmetrics electronic urine meter and a flow-through potassium ion-selective electrode (Ionetics) in the urine outflow. The screen display also gave the current status of the infusion pumps and their rates (ml h^{-1}), in addition to the current value of all the graphic displays.

Experimental procedure

Six dogs were anaesthetized with halothane and their lungs ventilated to a constant arterial $P\text{CO}_2$ of approximately 4 kPa. Sodium bicarbonate was given if the base excess of arterial blood deviated beyond -8, samples for blood-gas analysis being taken every 1 h. Two baseline plasma [K$^+$] measurements were made 30 min apart to ensure that plasma [K$^+$] and the electrode output were stable. A one-point calibration of the potassium electrode was then performed. The control system was switched on with a set-point of [K$^+$] = 4.5 mmol litre^{-1}. The time taken to achieve [K$^+$] > 4.45 mmol litre^{-1} was measured, and the set-point left unchanged for the next 2 h to assess the stability of the system. The set-point was then changed to [K$^+$] = 3.0 mmol litre^{-1}. The time taken to achieve [K$^+$] < 3.05 mmol litre^{-1} was measured, and the set-point again left unchanged for the next 2 h.

All data were stored in the IBM computer for further analysis, to yield the following: response time at each set-point, mean (SD) plasma [K$^+$] at each set-point (SD of 120 readings over 2 h). Other information available included the total amount of potassium chloride given to achieve and maintain the higher set-point; the amount of insulin given during maintenance of the higher set-point; the total amount of insulin given to achieve and maintain the lower set-point; the amount of potassium chloride given during maintenance of the lower set-point; total volume of fluid infused; total volume of urine excreted. The following may also be obtained in graphic form: plasma [K$^+$], urine flow, potassium excretion rate, total infusion rate, potassium chloride infusion rate and insulin infusion rate.

Two sets of controller constants were used (table I). In controller A the constants were relatively conservative and the concentration of infused potassium chloride was 50 mmol litre^{-1}, while in controller B the concentration of infused potassium chloride was 200 mmol litre^{-1}. A more concentrated infusion was used in the latter case to prevent infusion of large volumes of fluid, perhaps provoking a diuresis and loss of potassium. The glucose–insulin infusion was identical in each case. Three dogs were studied in each group.

TABLE I. *Controller constants for the "conservative" system (Controller A) and the "rapid" system (Controller B). P = Proportional; I = integral; D = differential*

	Controller A			Controller B		
	P	I	D	P	I	D
Potassium chloride (litre kg^{-1} h^{-1})	2	0.01	1	4	0.04	0.8
Glucose–insulin (litre-unit kg^{-1} $mmol^{-1}$ h^{-1})	1.2	0.05	0.6	4	0.08	1.8

TABLE II. *Performance criteria for the two controller systems (mean (range))*

	Controller A	Controller B
Initial plasma $[K^+]$ (mmol $litre^{-1}$)	3.47 (3.06–3.73)	3.32 (3.18–3.47)
Time to reach plasma $[K^+]$ = 4.45 (min)	79 (57–108)	22 (6–36)
Mean plasma $[K^+]$ at high set-point (mmol $litre^{-1}$)	4.43 (4.38–4.47)	4.35 (4.28–41)
SD at high set-point	0.083 (0.077–0.093)	0.0999 (0.061–0.142)
Time to reach plasma $[K^+]$ = 3.05 (min)	50 (43–56)	51 (33–71)
Mean plasma $[K^+]$ at low set-point (mmol $litre^{-1}$)	2.98 (2.90–3.03)	2.94 (2.88–3.01)
SD at low set-point	0.081 (0.067–0.103)	0.064 (0.032–0.091)

TABLE III. *Other information derived from the data available from this experiment*

	Controller A	Controller B
Potassium chloride given		
In reaching and maintaining $[K^+] > 4.45$ (mmol kg^{-1})	1.91 (1.13–3.20)	2.57 (1.76–3.40)
During maintenance of $[K^+] < 3.05$ (mmol kg^{-1})	0.50 (0.21–0.87)	1.24 (0.16–1.90)
Insulin given		
During maintenance of $[K^+] > 4.45$ (u kg^{-1})	0.118 (0.092–0.162)	0.249 (0.112–0.354)
In reaching and maintaining $[K^+] < 3.05$ (u kg^{-1})	1.594 (1.458–1.799)	4.911 (3.776–6.440)
Total volume infused (ml kg^{-1} h^{-1})	13.54 (8.34–16.85)	11.19 (7.83–16.12)
Total urine volume produced (mg kg^{-1} h^{-1})	5.31 (3.06–9.52)	13.63 (11.65–16.76)
Bicarbonate given during maintenance of $[K^+] < 3.05$ (mmol)	25 (20–30)	90 (50–120)

RESULTS

Electrode drift and interference were not a problem: recalibration was required, at most, twice during the 6-h experiment, and occasionally not at all. Synchronizing the two control equations when the concentration was near the set-point was not a problem, and the two infusions did not run simultaneously for longer than 3 or 4 min.

The performance criteria of the two controllers are given in table II. Mean resting plasma $[K^+]$ was similar in the two groups. The major difference in performance between the two controllers was in the response rate at the higher set-

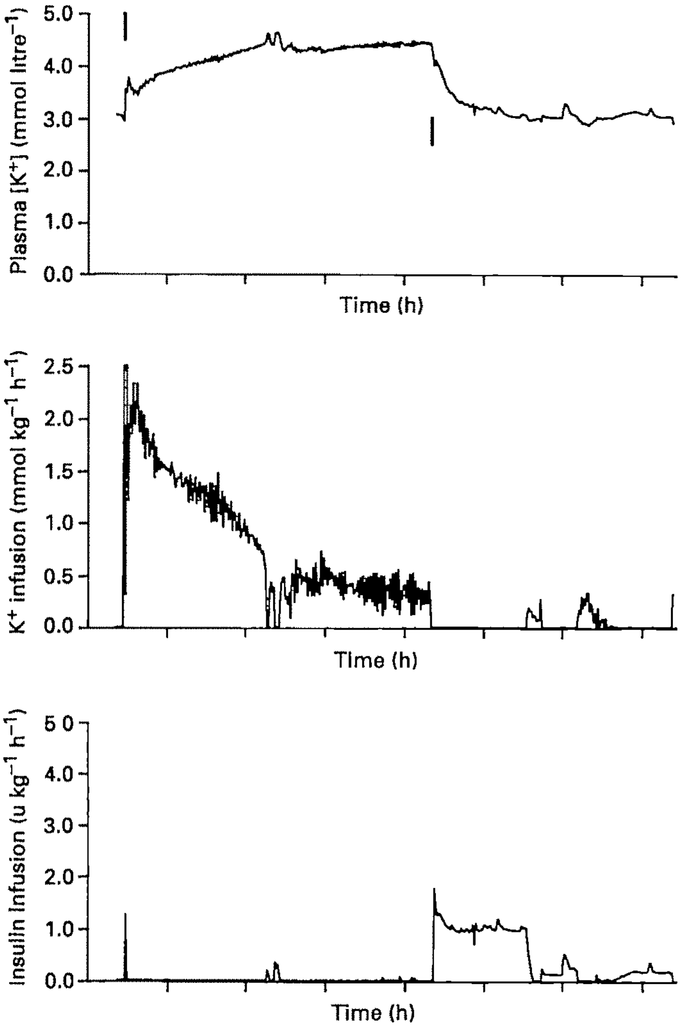

FIG. 4. Changes in plasma [K$^+$], K$^+$ infusion rate and insulin infusion rate during the experimental procedure using controller B. Vertical marks on the plasma [K$^+$] recording show when the set-point was changed.

point, controller B giving a considerably faster response. There was no marked difference between the two controllers in mean or SD [K$^+$] at either set-point, or in response rate at the lower set-point. Table III shows that controller B caused more side-effects at the lower set-point: urine output was inappropriately increased, more potassium chloride had to be given to prevent [K$^+$] decreasing to less than 3.0 mmol litre^{-1}, and more sodium bicarbonate had to be given to correct acidosis.

One example from each controller, showing changes in plasma [K$^+$] and potassium chloride and insulin infusion rates is given in figures 4 and 5.

DISCUSSION

Treatment of abnormalities of plasma [K$^+$] may be more difficult than it might appear. The rate of infusion of solutions (KCl or glucose–insulin) is difficult to predict, mainly because of individual variation in potassium distribution within the body. It is difficult to achieve an appropriate response without risking overshoot. Automatic control of plasma [K$^+$] using a feedback loop would be attractive, but requires continuous

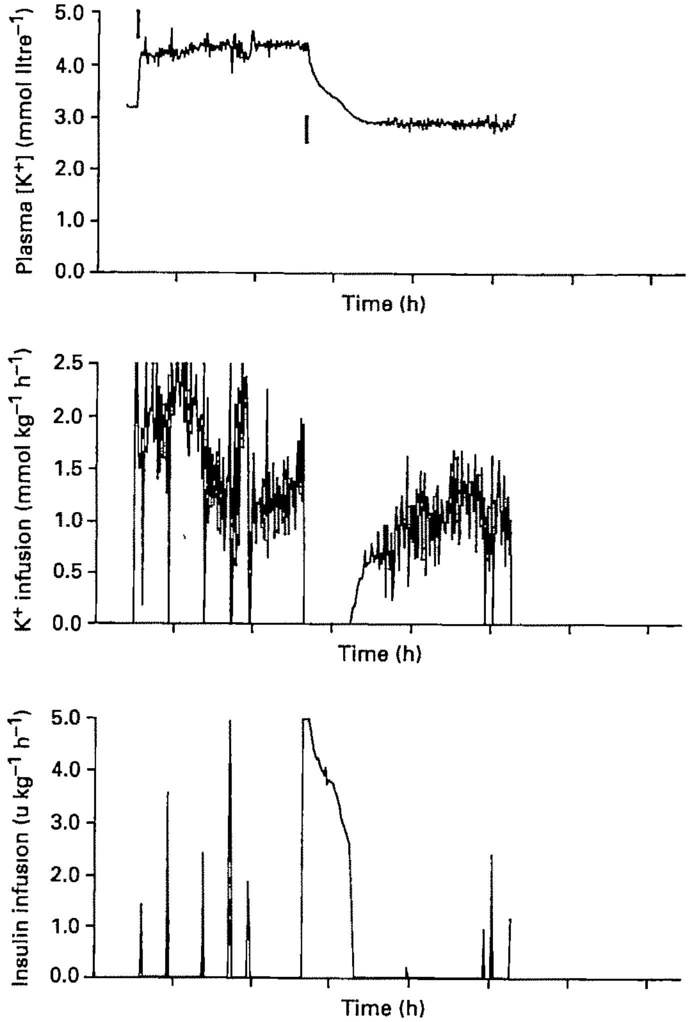

FIG. 5. Changes in plasma [K$^+$], K$^+$ infusion rate and insulin infusion rate during the experimental procedure using controller A. Vertical marks on the plasma [K$^+$] recording show when the set-point was changed.

monitoring of plasma [K$^+$], ideally in arterial blood. The catheter-tip ion-selective electrode used for this purpose is an established research tool [1, 3] and can give reliable, low-drift recordings for several hours [2]. The use of automatic computerized control systems has been explored for the control of administration of neuromuscular blockers [4], sodium nitroprusside [5] and volatile anaesthetics [6]. As far as we are aware, control of plasma electrolyte concentrations has not been described previously.

The results presented here show that such a system is possible to construct: monitoring of plasma [K$^+$] was reliable, relevant data may be stored, and stable concentrations of plasma [K$^+$] were achieved in healthy dogs. The controller constants of the system could be varied easily between wide limits, and two examples of different controller constants have been compared here.

The conservative system (controller A) increased plasma [K$^+$] to the higher set-point in about 1–1.5 h, with a gradually reducing rate of infusion of potassium chloride (fig. 4). This may represent too long a response time for some clinical situations. The rapid controller (B) gave a clinically realistic response time for increasing plasma [K$^+$] (10–30 min), but with a widely variable rate of infusion of potassium chloride and oscillations in plasma [K^+] (fig. 5). The maximum rate of infusion of potassium chloride (2.5 mmol kg^{-1} h^{-1}) was greater than that recommended normally for correction of hypokalaemia, but with the current system this rate is rarely maintained for more than 1 or 2 min. The consequences of the rapidly varying infusion rate and of oscillations in plasma [K^+] are not known, but provided plasma [K^+] is monitored continuously, they are probably safe. A shorter control interval (for example, 10 s instead of 1 min) would be one method of improving the stability of plasma [K^+].

The response rate of the glucose–insulin system for reducing plasma [K^+] was slower, as the response depended on a physiological action and not a simple chemical change. Also, the response rate was not increased by using the faster rates of infusion of insulin in controller B. Clearly, above a certain rate, the rate of infusion of insulin does not determine the rate of reduction in plasma [K^+], and the controller constants governing the insulin infusion could almost certainly be made even more conservative than in controller A. Indeed, a faster insulin infusion rate led to greater problems: urine output was inappropriately increased (probably an osmotic diuresis), more alkali was required to correct acidosis, and more potassium chloride was required to prevent plasma [K^+] decreasing to less than 3.0 mmol $litre^{-1}$. This last problem was surprising, as insulin is cleared from the circulation rapidly [7]. There is evidence [8] that the action of insulin on plasma [K^+] persists after it has been cleared from plasma, and the results presented here provide further evidence for this.

It seems that the controller constants governing the potassium chloride infusion may be varied within wide limits depending on the desired response rate. For example, controller B gives a response close to the fastest which would be clinically desirable, without undesirable overshoot but with possibly unacceptable oscillations; it is possible that these oscillations may be reduced or eliminated by using a shorter control interval. In contrast, controller A gave a smoother increase in plasma [K^+] without oscillations, but the change was too slow for many clinical situations. The system governing plasma [K^+] reduction behaved differently. The response rate of 50 min, described here, appears to be the fastest which can be achieved because of physiological limitations. There is probably an optimum infusion rate of the glucose–insulin mixture, which should be easy to define: it would certainly be no faster than the rate given by controller A (insulin 1 u kg^{-1} h^{-1}).

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British Journal of Anaesthesia 1991; **67**: 127–131

CORRESPONDENCE

TRANSFER OF PATIENTS BY HELICOPTER

Sir,—In their letter on Management of Major Trauma [1], Drs deMello and Restall made several adverse comments on medical helicopters which are at variance with the current situation in the U.K.

This is not the first time that it has been claimed that helicopters are dangerous and expensive [2], but not a single injury or fatality has been reported when civilian helicopters have been used for medical purposes in the U.K.; this compares favourably with the alternative land ambulance.

The cost of our system is £7 per mile, including staff and equipment, so that a transfer is equivalent to the non-recurring cost of only 2 or 3 days in intensive care. Currently, we are evaluating whether or not the benefits of helicopter transfer reduce treatment times and cost to the extent that there is an overall saving.

deMello and Restall's claim that interference between aircraft electronics and medical equipment requires consideration also shows a lack of knowledge of current regulations. The Civil Aviation Authority (C.A.A.) requires that all medical equipment is tested for interference before use in each aircraft. Interference is not, therefore, a problem in civilian helicopters.

Helicopters are safe and practical. It is not disputed that callout criteria need to be determined, but to this end the London Hospital's HEMS project is analysing each patient's outcome, the Department of Health is to review other primary systems, and the initial audit of our secondary project will shortly be submitted for publication.

Nevertheless, neither the medical profession nor the C.A.A. is complacent. A working party represented by the relevant colleges, specialist associations, the Department of Health and the C.A.A. has now set minimum standards for medical aspects of helicopter operations, and the C.A.A. has produced its own document of requirements for the aviation aspects.

A. Bristow
London

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Sir,—Thank you for the opportunity to respond to the comments of Dr Bristow. I am grateful for the information on the current regulations laid down by the Civil Aviation Authority.

Our comments on the disadvantages of helicopter transfer [1] were based on our experiences over 10 years at home and abroad; and more recently in the Gulf. The RAF provides the aeromedevac service for the military, but occasionally we (as Army anaesthetists) have been involved directly or indirectly in such a service. The helicopters used are not designed specifically for medical purposes, as they also perform other military tasks. Thus we were keen to know how the difficulties we had experienced had been solved or minimized by Dr Bristow's team. Flight surgeons in the Gulf to whom I have spoken have had similar experiences. The problems of the biodynamics of aerial transfer, thermal stresses, motion sickness, etc. are well documented [2].

In our opinion, the use of helicopters in the United Kingdom would include long distance transfers, "scoop and run" sorties to and from isolated areas, transfer of organs for transplantation, and the transfer of *stable* critically ill patients to a supraregional or national facility. It is the last category that we believe still needs to be evaluated and defined. However, more emphasis ought to be placed on land ambulances (in terms of numbers, staffing, equipment scales and expertise), as only a minor proportion of the trauma workload will be met by helicopters.

I do not have the running and capital costs of comparable schemes in the U.K., so I cannot comment on the cost-effectiveness of the scheme. We look forward to further information, so that our patients may benefit from the work done by our civilian colleagues.

W. F. deMello
Aldershot

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DEEP VENOUS THROMBOSIS AND ANAESTHESIA

Sir,—In the January issue of *British Journal of Anaesthesia*, there appeared both an editorial by Dr Peter McKenzie [1] and an original article by Jorgensen and colleagues [2] on the subject of deep venous thrombosis and anaesthesia.

My own studies were quoted frequently in both these articles, but I was concerned to note that both my studies [3, 4] had been quoted incorrectly.

In the study by Jorgensen and colleagues [2], they stated "However, Modig and colleagues did not find a significant reduction in the incidence of total DVT" and in the editorial it was stated "In both his major studies, Modig did not report the total DVT incidence, but he subdivided the incidence of thrombi into popliteal and femoral *vs* calf and thigh in the 1983 study [3], and thigh *vs* thigh and calf in the 1986 study [4]."

I think it is important to correct these statements. In the 1983 study, it was observed in the results section quite clearly that "the frequency of deep venous thrombosis involving both the calf and thigh veins was significantly lower in patients receiving continuous epidural anaesthesia (12 of 30) than in those receiving general anaesthesia with parenteral analgesics postoperatively (23 of 30)." In the latter study [4], of 94 patients undergoing total hip replacement, it was also stated clearly in the results section that "the frequency of DVT involving both the thigh veins and calf veins was significantly lower in the epidural group than the corresponding frequency in the general anaesthesia group."

J. Modig
Uppsala

Sir,—In the editorial "Deep Venous Thrombosis and Anaesthesia" [1] and in our paper "Antithrombotic Efficacy of Continuous Extradural Analgesia after Knee Replacement" [2] published recently, it was stated that Dr Modig and colleagues [3, 4] did not find a significant reduction of the total incidence of deep vein thrombosis when comparing extradural and general anaesthesia in patients undergoing hip surgery. However, we have since realized that the term used by Modig and colleagues: "the frequency of deep venous thrombosis involving both the calf *and* the thigh veins" was equivalent with the total incidence of deep venous thrombosis—that is, involvement of the calf *or* the thigh. Thus Modig and colleagues did indeed demonstrate a significant reduction in the total incidence of deep venous thrombosis.

L. N. Jørgensen
Copenhagen

Sir, —Thank you for the opportunity to reply to the letter from Dr Modig. As I consider him to be a key worker in the field of deep venous thombosis (DVT) and anaesthesia, his comments deserve a detailed reply.

I wish first to state a philosophical point which may partly explain our apparent differences of interpretation of his work. I consider that the primary question to be answered in any study of DVT is to know the number of patients with DVT, whatever the site of DVT. Clearly, at the time of investigation, if a patient does not have a DVT, they cannot have a pulmonary embolus, unless a DVT develops subsequently. A major and extensive DVT may be a densely adherent and organized clot and pose little threat of embolism. However, an apparently minor clot in any site in the deep veins may propagate and embolize.

For these reasons, I consider the *total* incidence of DVT, and also incidence of normal venograms, to be the most important finding in any such study. In my editorial [1] I stated that "in both his major studies Modig did not report the total DVT incidence". I consider this statement to be correct, but that might depend on one's interpretation of the meaning of "report". Nowhere in the text or tables is there any mention of total incidence, in either wording or numbers. However, in the first study [3], there are two complex figures from which it is possible, with difficulty, to derive the raw data, thus enabling the calculation and analysis of total DVT incidence. I confess that I had not done this previously, as I had assumed that Modig would have done this and, as it was not mentioned, that there was no important, or statistically significant, result. This presumption was strengthened further by the fact that Modig had gone on to conduct a larger study [4], strongly suggesting that the first had been inconclusive.

To my suprise, my analysis of the raw data shows a most conclusive and important result, as follows: Number of patients after GA developing DVT = 23, no DVT = 7. Number of patients after extradural developing DVT = 12, no DVT = 18. 2×2 Chi-square analysis with Yates' correction yields $P < 0.01$.

This implies, therefore, that the study in 1983 which was the first published, prospective, randomized study using impeccable methodology, contains a most important result which was never stated or, apparently, analysed. I therefore have to change my conclusions about the research from "highly suggestive but not proven" to "almost certainly proven". What I would wish now to learn from Modig and his colleagues is:

First, why did they not report and analyse this highly important finding?

Second, what was the total incidence of DVT in each group in the later, larger study?

I do hope that this reply puts the record straight.

P. J. McKenzie
Oxford

Sir,—Thank you for the opportunity of allowing me to comment in the same issue of the Journal to the letters by Dr McKenzie and Jørgensen, responding to my first communication. I am very pleased that my groups' research studies have been put into correct perspective.

Dr McKenzie raises several questions. First, why did we not follow up our study published in 1986 [4]. The reason for this is simply that in our first study, published in 1983 [3], we were criticized for our use of preoperative bilateral phlebography, as it has been claimed that this method has a potential for inducing thrombosis. Thus preoperative phlebography was omitted in the study of 1986.

The other questions raised by Dr McKenzie are largely semantic.

I am very pleased indeed to see that this question is now settled. It is clearly now agreed that our studies, together with that published by Dr Jørgensen, strengthen the conclusion that extradural anaesthesia in total hip replacement and total knee replacement is associated with a significant reduction in the incidence of deep vein thrombosis compared with general anaesthesia.

J. Modig
Uppsala

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PHARMACOKINETICS OF ATRACURIUM

Sir,—We congratulate Drs Beemer, Bjorksten and Crankshaw on their description of the pharmacokinetics of atracurium [1]. As they observe correctly, the derivation of pharmacokinetic parameters after a single bolus dose is subject to difficulties because of the presumed degradation of atracurium in sites peripheral to the plasma.

In our view, however, the crucial flaw in previous attempts to describe the pharmacokinetics of atracurium (including our own, [2]), is not that the observations were not made at steady state, but that it is impossible to define the rate of peripheral degradation of atracurium on the basis of measurements made on plasma samples alone [3]. The application of standard formulae allows an objective summary of data, and comparison between groups, and may thus be useful. It does not allow calculation of the *plasma* clearance or steady state volume of distribution as usually defined [4].

We wish to point out that the method of analysis used by Beemer and colleagues does not overcome the problems created by the peripheral degradation of atracurium. The application of his equation (3) gives an estimate of clearance which is *not* equivalent to plasma clearance, defined as the volume of plasma theoretically completely cleared of drug per unit time. Indeed it may be re-written:

$$\text{Clearance} = \frac{\text{Rate of drug degradation from the plasma}}{C_P^{ss}} + \frac{\text{Rate of drug degradation outside the plasma}}{C_P^{ss}}$$

Only the first of these terms represents the *plasma* clearance. Moreover, the authors then apply this value for clearance (obtained at steady state) when calculating the amount of drug eliminated during the first 1 h of drug administration. Their equation (6) refers, however, to data gathered during the whole of the first 1 h (much of which was not close to a steady state), for which this value is therefore not applicable. One might correctly write, instead of equation (6):

$$\begin{aligned}&\text{Amount of drug eliminated} = \textit{from the plasma}\\ &\qquad\text{during 1 h} = \text{Plasma clearance} \times \text{AUC}_{0\text{–}1}\end{aligned}$$

Unfortunately, the amount of drug eliminated from sites peripheral to the plasma, and hence the total amount of drug eliminated from the body, remains unknown, for the data pertain only to the plasma.

Whilst Beemer, Bjorksten and Crankshaw have obtained an estimate of V^{ss} smaller than that produced by several other groups, it may be noted that the problems of defining a pharmacokinetic model for atracurium have been attacked more explicitly by Fisher and colleagues [5], albeit with the assumption that spontaneous degradation of atracurium occurs throughout the body at a rate comparable to that in plasma *in vitro*. The latter group obtained values of V^{ss} considerably less than 130 ml kg^{-1} in four of their five patients.

C. J. R. Parker
J. M. Hunter
Liverpool

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Sir,—We thank Drs Parker and Hunter for highlighting the problem of defining pharmacokinetic terms, particularly as it applies to clearance, and indirectly raising the issue of the goals of pharmacokinetic studies.

We believe that one of the primary aims of pharmacokinetic studies is to derive data to improve the accuracy of drug administration and that the studies should not be considered an end in themselves. Our study derived the pharmacokinetic variables, total clearance and "apparent" V^{ss}, which are required to design infusion regimens to establish and maintain a given plasma concentration of atracurium [1,2]. By contrast, the technique used by Fisher for defining a more "physiological" model has led to difficulties, such that the derived pharmacokinetic variables do not appear to describe accurately the pharmacokinetics of atracurium when administered by continuous infusion [3,4].

In our study we did not measure the plasma clearance of atracurium, but rather the total or systemic clearance of atracurium at steady state. We referred to this as the clearance of atracurium. Unfortunately, confusion may have arisen as figure 1 was incorrectly labelled "plasma clearance".

The total clearance of atracurium, as Drs Parker and Hunter correctly state, is the sum of the clearance from the plasma and the periphery. For a drug such as atracurium, which can be described by a two-compartment model, and which is cleared from both the central (plasma) and peripheral compartments [5], the total clearance can be defined as:

$$\text{Total clearance} = \text{plasma clearance} + x(C2/C1)\text{peripheral clearance}$$

where x = a constant; $C1$, $C2$ = concentrations of atracurium in the plasma and the periphery, respectively. At steady state,

$$x(C2/C2) = 1$$

The total clearance of atracurium is time dependent, because of the time required for atracurium to equilibriate with the periphery. Unfortunately it is impossible to measure $C2$ or to estimate x accurately with any method, without making assumptions as to the rate of peripheral clearance of atracurium.

The apparent V^{ss} was estimated in our study by assuming a constant total clearance of atracurium. We believe that this should not introduce a significant error because of the rapid distribution half-life of atracurium which has been estimated to be as short as 1.5 min [2]. For a 1-h infusion, this should introduce only a very small error. An error of this type usually occurs in the estimation of V^{ss}, as clearance is considered to be constant for drugs excreted from the central compartment.

This is based on the incorrect assumption that the central compartment is homogeneous and that instantaneous mixing occurs within it [6].

G. H. Beemer
A. R. Bjorksten
D. P. Crankshaw
Melbourne

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IDENTIFICATION OF THE INTERPLEURAL SPACE

Sir,—We were interested to read the paper by Dr Scott in which he described a technique to locate the interpleural space using a saline infusion [1]. The same principle is applied in the "falling column" sign—a method we described previously to locate the interpleural space [2]. In this technique, a syringe barrel with the plunger removed is filled with several millilitres of saline and attached to a Tuohy needle. As the needle is advanced, correct placement in the interpleural space is signified as the column of fluid falls away as saline is "pulled" into the interpleural space. A stopcock may be interposed between the needle and syringe to prevent entry of air during the interval between needle placement and catheter placement.

It would appear that both the falling column and saline infusion methods provide a clear and distinct end-point for identifying the interpleural space, and thus should minimize the incidence of pneumothorax from needle misplacement. The cases of pneumothorax reported in the literature were associated with mechanical ventilation [3,4] or, in one case, unexpected movement by the patient [5]. We prefer, therefore, to insert interpleural catheters in awake, spontaneously breathing patients. The interpleural pressure remains negative throughout the ventilatory cycle and the need for disconnection of the ventilator is obviated.

The use by Dr Scott of the catheter sheath adaptor through which the catheter passes is to be commended, as it would appear to eliminate altogether the risk of entry of air into the interpleural space.

E. Lee
Nashville
B. Ben-David
Haifa

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Sir,—I thank Drs Lee and Ben-David for their comments and apologize for having missed, in an early literature search, the "falling column" sign.

Their letter and my own publication signal an unease within the specialty about the current means of producing interpleural analgesia by the deliberate introduction of air into the pleural cavity. It would be unfortunate if, by creation of an iatrogenic pneumothorax, a new and—in selected patients—valuable technique were brought into disrepute.

P. V. Scott
Redditch

HEADACHE AFTER CONTINUOUS SPINAL ANAESTHESIA

Sir,—We read with interest the paper by Kestin and colleagues [1] comparing continuous spinal with extradural anaesthesia for elective Caesarean section. The use of continuous spinal anaesthesia for these patients is not new, but it has never achieved great popularity, presumably because of the high incidence of postoperative spinal headache; Giuffrida and colleagues [2] quoted an incidence of 16% using a 21-gauge catheter. It was disappointing to note that the use of a 26-gauge needle and 32-gauge spinal catheter was associated with a 10% incidence of headache.

We observe, however, that it is possible to thread the 32-gauge catheter through a 24-gauge pencil-pointed Sprotte needle. This is a variation on the older Whiteacre needle. A recent study found no postoperative headache in a series of 55 obstetric patients given spinal injections through these needles [3]. This, rather than smaller, diamond-tipped needles, may be a more fruitful avenue of research in attempting to reduce further the incidence of headache, while maintaining the undoubted advantages of a continuous spinal anaesthetic technique.

K. R. Milligan
H. Carp
Belfast

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Sir,—Thank you for the opportunity of replying to the letter from Drs Milligan and Carp. In our study, there were two of 20 mothers in the spinal group with a headache typical of that after lumbar puncture. The headaches were mild, discovered only by direct questioning, and the mothers did not need to restrict their activity. Two other mothers in the spinal group, and three in the extradural group had headaches that were not typical of lumbar puncture headache, but had symptoms at least as severe as the two "spinal" headaches. In our small study, spinal headaches were not a significant clinical problem.

The 32-gauge catheter can be threaded through a 24-gauge Sprotte needle, but the hub design of those currently available is not suitable for this purpose. Modified 24-gauge Sprotte needles for the 32-gauge catheter will be available from the manufacturer (Rusch U.K.) in the next few months. There are technical difficulties in threading the 32-gauge catheter through 26-gauge needles using a midline approach [1]. In our study, we had no difficulty using an oblique paraspinous approach. A 24-gauge Sprotte needle may overcome these technical difficulties and reduce the incidence of spinal headache, but this remains to be determined.

I. G. Kestin
Bristol

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MIDAZOLAM AND ERYTHROMYCIN

Sir,—I was interested to read the clinical report by Hiller and colleagues describing unconsciousness associated with the use of midazolam before erythromycin given for antibiotic prophylaxis before adenoidectomy [1]. The plasma concentration of midazolam was greater in this patient than in six other children who did not receive erythromycin. Erythromycin has been shown previously to inhibit the metabolism of theophylline [2] and alfentanil [3].

It has been determined that elimination of the immunosuppressive drug, cyclosporine, depends on its metabolism in the liver by cytochrome P450 IIIA [4]. Cytochrome P450 IIIA also catalyses the N-demethylation of erythromycin and the erythromycin breath test (the ability of the patient to demethylate erythromycin to produce exhaled ^{14}C-carbon dioxide after i.v. ^{14}C-N-methyl-erythromycin) has been used as a predictor of blood concentrations of cyclosporine in patients [4,5]. When the erythromycin breath test was administered to 30 hospital inpatients, there was a four- to six-fold range of breath test values, indicating marked inter-individual variability [4]. Thus for cytochrome P450 IIIA there appears to be a broad unimodal distribution of enzyme activity in the population, in contrast with the bimodal distribution of enzyme function seen in debrisoquine genetic polymorphism, in which the ability to metabolize debrisoquine is impaired in 8–10% of the Caucasian population (poor metabolizers).

There is *in vitro* evidence that midazolam also is metabolized by cytochrome P450 IIIA [6,7]. Midazolam itself shows considerable variation in its pharmacokinetic parameters, possibly resulting partly from genetic polymorphic drug metabolism. I suggest, therefore, that the increased concentration of midazolam in the patient described in the case report by Hiller and colleagues was a result of inhibition of cytochrome P450 IIIA, perhaps in a patient with reduced cytochrome P450 IIIA function.

M. Wood
Nashville

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British Journal of Anaesthesia 1991; 67: 132–133

BOOK REVIEWS

Regional Anaesthesia in Children, 1st Edn. Edited by C. Saint-Maurice and O. Shulte Steinberg. Published by Medi Globe SA, Fribourg. Pp. 200; indexed; illustrated.

There are very few anaesthetists still in active practice who can remember the days before tracheal intubation, neuromuscular blocking agents and halothane revolutionized general anaesthesia. Local anaesthetic techniques were then an essential part of the skilled practitioner's armamentarium. Improvements in general anaesthesia led to a generation of anaesthetists who rarely used regional techniques, and a generation of surgeons unwilling to tolerate some of the limitations they impose. This was particularly the case in the paediatric field, where few patients allow operation under regional anaesthesia alone, supplementary sedation or light general anaesthesia usually being necessary.

Over the past decade, the advantages of regional techniques have achieved greater recognition, with their ability to reduce intra- and postoperative morbidity and provide excellent analgesia. Several textbooks of adult regional anaesthesia have appeared, but there has been little in the paediatric field until now.

Saint-Maurice and Shulte Steinberg have assembled a team of 12 authors to write this text; eight are French, but there are also contributions from Germany, Italy, Belgium and Australia. The only English contribution is the language co-ordination by Armitage.

The format follows expectations, with chapters on basic principles, history, anatomy, physiology, pharmacology and equipment preceeding the chapters on individual techniques. The book is rounded off with chapters on postoperative and chronic pain management and a section on uncommon diseases and special problems. The introductory chapters account for some 40% of the total number of pages and provide an excellent background, particularly where they concentrate on the differences between children and adults; however, much of the information may already be familiar to most anaesthetists from adult texts.

The chapters on techniques cover the wide range of European practice which seems little different from that in the U.K., although few British anaesthetists are regular users of chloroprocaine, mepivacaine or etidocaine, none of which is readily available in the U.K. Many of the authors highlight the problems peculiar to performing the blocks in children and this is of great value.

Inevitably, with multiple authors, there is a tendency for information to be repeated in different sections and occasionally there is conflicting advice. More rigorous editing would have avoided this. There is also a surprising lack of information on the use of head and neck blocks. The value of spinal and extradural opioids receives little mention.

The style of the superb medical illustrations may be familiar to many readers, having been drawn by Paul Buckhoj who was responsible for the pictures in Eriksson's *Illustrated Handbook in Local Anaesthesia*. Sadly, many of the diagrams and photographs have inadequate or absent legends, so that they are merely pretty pictures which do little to amplify the text. For a few it is impossible to deduce any relevance at all. There is also a surfeit of hyphens in the text where none should exist. It is impossible to know if this is caused by inadequate proof reading or by the book's being printed in Singapore.

These criticisms should not detract from the fact that this is a very readable book which is a valuable addition to the paediatric anaesthetic literature, written by a group of committed, enthusiastic doctors whose dedication to the improvement of the welfare of children cannot be questioned.

J. Wandless

Medical Statistics on Microcomputers, 1st Edn. By R. A. Brown and J. Swanson Beck. Published by BMJ, London. Pp. 103; indexed; illustrated. Price £8.95.

This small introductory guide to medical statistics shares many features with its older sibling *Statistics at Square One*, also published by BMJ. *Medical Statistics on Microcomputers* consists of a series of articles reprinted from the *Journal of Clinical Pathology*, and the subject matter used in the examples necessarily reflects this origin. The style of presentation is relaxed and fluid and may be recommended to those who have avoided referring to statistical texts after initial experience with more mathematically orientated volumes. The authors have chosen throughout the book to illustrate discussions of commonly used statistical techniques with examples based on two widely used microcomputer programs, Minitab and Statgraphics. Whilst this choice inevitably limits the scope of some of the discussion, it does allow many readers to follow the examples given and investigate further possibilities for analysis of the data. Those whose departments use other statistical programs may find the concentration on these two packages somewhat frustrating.

Initial chapters cover data handling on computers, methods of data summary, and simple two-group comparisons. The information given on "data handling" is rather sketchy, as any attempt must be to do justice to such a broad subject heading in 10 pages. A clear discussion of pitfalls in graphical presentation of data in the following chapter is to be recommended, particularly for its discouragement of the common but misleading "mean plus or minus two standard errors" method. The following chapters offer concise explanations of methods for multiple group comparisons, handling of non-normally distributed data, correlations, categorical data and methods for use in the design of diagnostic tests. The last is particularly welcome, covering a subject discussed less frequently in elementary statistical texts.

Rather than simply offering the reader a list of statistical tests, the authors suggest approaches applicable to the analysis of various kinds of data and define clearly the limitations of each technique. Despite this, the reader is encouraged to seek further information before deciding firmly on one particular method. Unfortunately, a rather short bibliography at the end of the book is only sparsely referenced in the text. The references given are generally to practical rather than purely theoretical publications, in keeping with the authors' approach throughout the book.

Some criticism may be levelled at all texts of this kind, in that they may encourage the reader to believe that statistics is a field which can be approached only via a computer or by reference to a local "statistical guru". This approach may perpetuate a certain amount of unwarranted fear of what are sometimes relatively simple mathematical techniques. These criticisms apart, the authors have achieved their apparent aim in producing a clear and concise introduction to practical medical statistics suitable for those planning relatively simple experimental studies.

S. Mottram

Postanaesthetic Care. Edited by E. A. M. Frost and P. L. Goldiner. Published by Prentice Hall, Hemel Hempstead. Pp. 318; indexed; illustrated. Price £56.95.

The majority of anaesthetic and surgical problems encountered in the post-anaesthetic period are considered in 19 well referenced chapters. Particularly good are the chapters on Infection Control, Respiratory Care, The Obstetric Patient, and The Cardiovascular Patient. Post-anaesthetic care of the transplant patient is considered in a separate chapter and will prove useful, as such patients present in increasing numbers for unrelated surgical procedures in centres where staff have not had extensive experience with the problems encountered in these patients. A refreshing strength of this text is that repetition of subject matter in different chapters is kept to a minimum.

Unfortunately, there are frequent digressions from the subject of the book toward intraoperative anaesthetic care. Six pages of the chapter on the ambulatory surgery patient are devoted to anaesthetic technique, while only five follow the heading "Recovery from Anaesthesia and Discharge". Also, poor editing and a wide variation in quality among different chapters prevent this from being a comprehensive text able to stand alone. For instance, errors such as recommending a postoperative dose of fentanyl 5–10 μg kg^{-1} for children are not uncommon. An example of the occasional tendency toward dogma is the statement in the first chapter that "It is routine practice ... that patients spend at least an hour in the (Recovery room)". As there are no data given to support this notion, the British anaesthetist, who may well disagree, will be left unimpressed. The chapter on postoperative pain contains a lengthy discussion on spinal opioids, but there is no mention of any advantages compared with traditional techniques. Furthermore, no reference is made to the care of patients with extradural or subarachnoid catheters. Nurses specializing in recovery room care would no doubt appreciate such information. The value of this text to readers in the U.K. is diminished by segments that focus on practice and drugs more or less restricted to the U.S.A. (for example, magnesium sulphate as part of the treatment for PET).

In summary, despite faltering occasionally, this book is a most useful adjunct for anaesthetists, nurses and those on either side of the Atlantic who care for patients in the post-anaesthetic period.

B. Davis

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 8th Edn. Edited by A. G. Gilman, T. W. Rall, A. S. Nies and P. Taylor. Published (1990) by Pergamon Press, plc, Oxford. Pp. 1811; indexed; illustrated.

It has been 5 years since a new edition of this pharmacological bible, and its arrival is welcomed. The book was first published 50 years ago and it has expanded enormously over the years.

There are many changes in this edition, and several new authors have been recruited. There are new chapters on the principles of toxicology and drugs affecting the gastrointestinal tract, immunological system and the skin. All the existing chapters have been updated and many have been reorganized completely. The book now contains 1811 pages and is an essential source of reference for all those involved in pharmacology, including anaesthetists. It achieves its aim of reviewing succinctly all drugs used in modern medical practice and cites many key references.

Chapters on drugs used in anaesthesia are well written, but not as comprehensive as most specialized texts. However, the discussion of drugs affecting the autonomic nervous system is excellent and well worth reading in preparation for basic science examinations in anaesthesia.

This latest edition of one of the standard pharmacological textbooks has continued the excellent tradition. It is highly recommended for all anaesthetic or intensive care libraries.

D. J. Rowbotham

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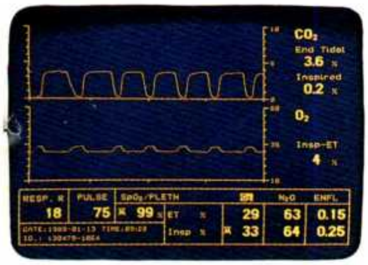

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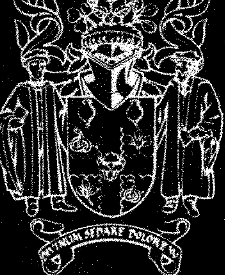

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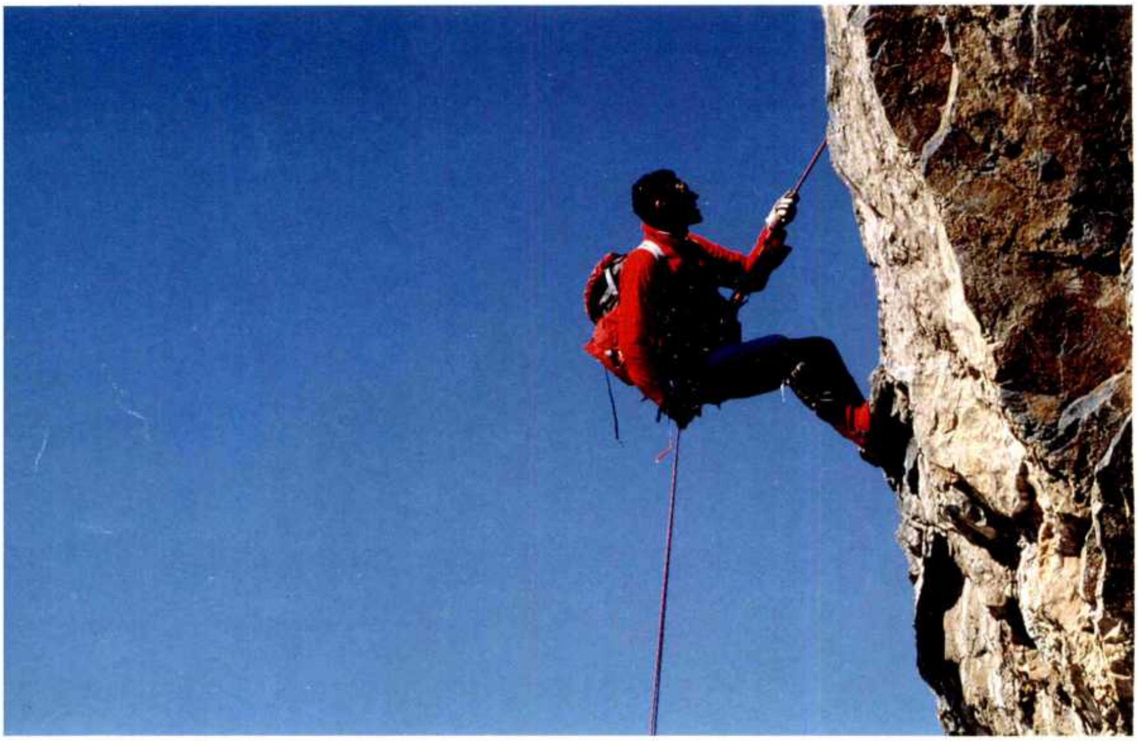

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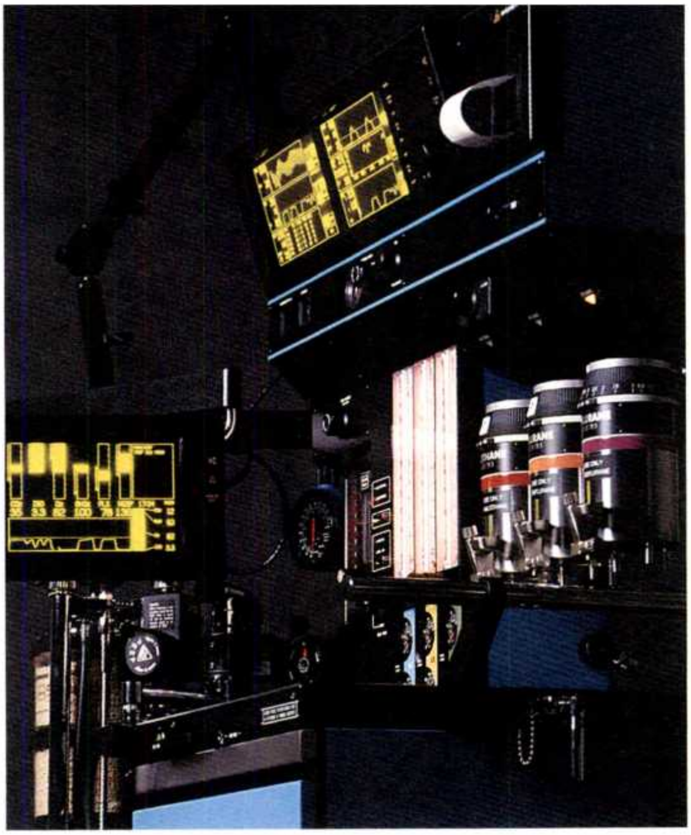

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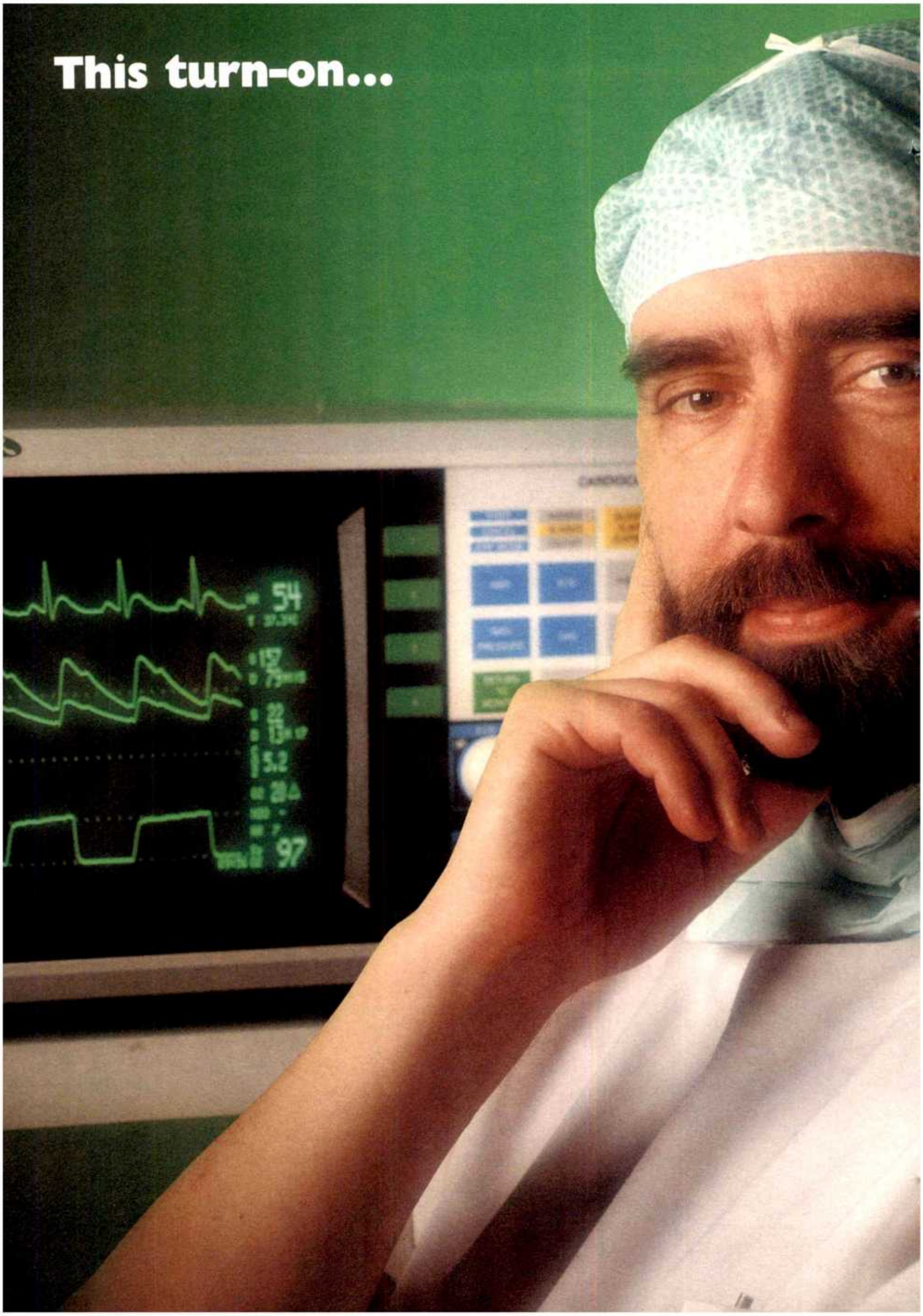
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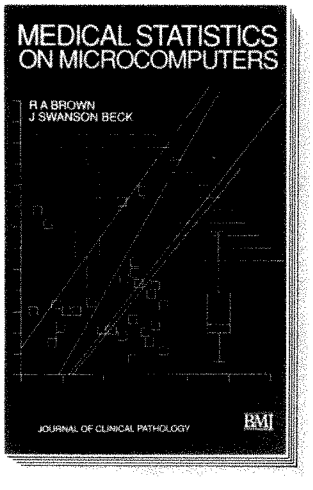
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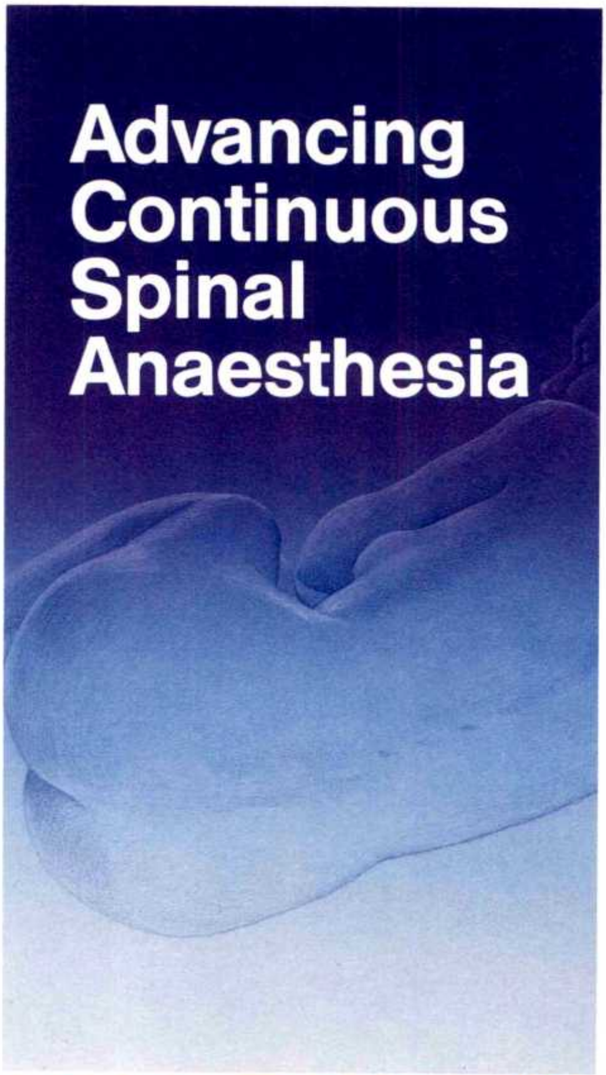

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 67, No. 2 AUGUST 1991

EDITORIAL

FLUID AND ELECTROLYTES REVISITED

The College of Anaesthetists' scientific meeting in May 1990 brought an area of everyday practice relating to fluid and electrolyte balance, which many believe to be mundane, into high profile and exploded some of our cosy myths with well validated new facts. New agents for the management of metabolic acidosis will shortly become available for general use and their rational application will be a matter of great importance.

This issue of the Journal is based on that scientific meeting, which aimed to challenge old concepts in acid–base, sodium, potassium and calcium balance and to debate the choice of fluids for resuscitation and for prevention of perioperative renal failure.

Cohen presents a radical revision of the traditional explanations for acid excretion, elaborating the key role of the liver in this respect [4] and drawing on the work of Häussinger, Steeb and Gerok [7] showing that in liver disease, particularly cirrhosis, plasma bicarbonate concentration is related inversely to the ability of the liver to synthesize urea. In renal failure, by contrast, the uraemic acidosis is most probably related to failure of nitrogen excretion as NH_4^+ by the kidney and its conversion to urea by the liver, with production of protons producing acidosis [2]. Whatever the mechanisms of production of acidosis, we must revise our views of its automatic, unthinking treatment with sodium bicarbonate, which in many experimental and clinical studies has been shown to worsen intracellular acidosis related to hypoxic ischaemic conditions [1, 10].

It is hard to believe that so much controversy has raged in the past decade over the question of whether hyponatraemia *per se* or its excessively rapid correction is responsible for neurological damage; either central pontine myelinolysis or cerebral oedema and hypoxic damage. The meticulous clarification by Swales repays careful reading. New, but not clarifying, information is available describing the development of fatal diabetes from untreated hyponatraemia [5] and the importance of the speed of onset in the management of hyponatraemia [3], if necessary by urgent measures such as continuous arteriovenous haemofiltration before liver transplantation [8]. Time will tell whether the sex differences which result in increased morbidity from hyponatraemia in female rats apply also in the human female [6]. Less controversy surrounds the maintenance of potassium balance in the perioperative period, but a sound update is provided by Vaughan.

Recommendations concerning appropriate fluids for resuscitation are beginning to be questioned now that high molecular weight starch solutions are available and hypertonic saline solutions are finding a place. Anxieties raised by the occurrence of acute hyperosmolality after administration of sodium bicarbonate solutions and its relation to high mortality and brain damage should make us question the potential adverse effects of hyperosmolar fluid loading with hypertonic saline on cerebral haemodynamics. It is likely that hypertonic saline exerts reflex and venoconstrictor effects in addition to osmotic effects which may be beneficial in resuscitation of hypovolaemic patients. Nevertheless, the advice of Mattar [9] that "the hypovolaemic patient needs volume not a quick fix" is apt.

On the question of preventing postoperative oliguria, more questions are raised by our conventional answers and we are repeatedly faced with the difficulties of assessing body fluid status from limited access to major body fluid compartments.

Erdmann brings an excellent perspective into the question of calcium usage in resuscitation by bringing his own work to challenge our current (and recently revised) recommendations.

Long may we continue to examine this major area of our practice, explode old myths and explore innovations.

S. M. Willatts

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IS POSTOPERATIVE OLIGURIA AVOIDABLE?

P. SWENY

Postoperative salt and water retention has been recognized for most of this century. Does it matter? Can or should it be avoided? These are still questions about which debate continues.

Pringle, in 1905, observed reduced urine volumes and weight gain in postoperative patients [31]. Wilkinson studied 27 patients perioperatively and observed a decrease in urinary concentrations of sodium and chloride despite i.v. and oral fluids, and concluded that sodium retention was not the result of reduced intake, but was an unavoidable response to surgery [43]. Moyer recorded a marked reduction in the urinary excretion of water, chloride, sodium and urea [28]. He recommended avoidance of the use of glucose solutions while the period of reduced water excretion lasted, giving saline only if signs of deficit occurred or there was evidence of abnormal extra losses. In 1953, Le Quesne showed that sodium and water retention occurred postoperatively whether or not sodium supplements were given. A weight gain of about 2 kg was seen in his patients, even in those given no sodium supplements. These patients were unable to produce a hypotonic urine [21]. Early attempts were made to accommodate this salt and water retention by curtailing fluid intake and by 1952 the view had arisen, particularly in Europe, that fluid restriction in the perioperative period was important [24].

The opposing view was proposed by Shires in the early 1960s on the basis of studies with isotopically labelled sulphate, albumin and tagged red blood cells, which showed a contraction in the extracellular fluid volume that could not be accounted for by measured losses. This was interpreted as being a reduction in the so-called "functional extracellular fluid volume". This reduction was felt to occur because of sequestration of fluid in "third spaces", for example traumatized tissue, dilated gut and the peritoneal cavity. It was felt that the lost fluid represented a loss to the body's economy and should be compensated for by adequate perioperative fluids [36, 37]. In North America, in general, liberal and sometimes excessive quantities of fluid were given while in Europe, particularly in the United Kingdom, fluids were restricted severely. The controversy became so extreme that the two principal protagonists wrote a joint Editorial urging moderation [25]. They recommended use of a balanced salt solution (Hartmann's or Ringer's lactate) to replace losses and sequestration of fluid in the perioperative period, but emphasized that blood losses should be replaced with blood. A further recent element has been added to the debate by consideration of the type of fluid that should be administered—colloid or crystalloid [41].

This article reviews the neurohumoral pathways that regulate salt and water balance and discusses the stimuli leading to perioperative salt and water retention. Clearly, a sensible fluid regimen must avoid overhydration during the phase of salt and water retention, as this may lead to pulmonary oedema and hyponatraemia. Conversely, too sparing an approach may well increase the incidence of postoperative acute renal failure. In addition, an inappropriate choice of fluid may lead to systemic or pulmonary oedema and hyponatraemia. The issue is really whether or not oliguria is a physiological response to perioperative hypovolaemia, and therefore both undesirable and avoidable. The alternative is to suggest that postoperative oliguria is an un-

KEY WORDS

Fluid balance: oliguria Complications oliguria. Ions. sodium, chlorine. Hormones aldosterone, antidiuretic Kidney. function

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TABLE I. *Factors regulating reabsorption of sodium and water. ANP = atrial natriuretic peptide; AII = angiotensin II; AVP = arginine vasopressin*

Agent	Actions
ANP, AII Macula Densa Cl^-/Na^+	Alterations in GFR
Changes in peritubular physical forces	Regulation of proximal tubular Na^+ and water retention (isosmotic) Variation in distal solute delivery
Sympathetic innervation	Increased tubular reabsorption of Na^+ Increased release of renin Cortico-medullary shunting
AVP	Increased thick ascending limb reabsorption of Na^+ Increased distal reabsorption of water
Aldosterone	Increased distal reabsorption of Na^+
ANP	Reduced distal reabsorption of Na^+

avoidable response to the stress inherent in anaesthesia and surgery which cannot be overcome by simple fluid loading.

REGULATION OF SALT AND WATER BALANCE

Regulation of salt and water balance is synonymous with regulation of the extracellular fluid volume. Table I summarizes the principal mechanisms responsible for the regulation of salt and water balance, which also are illustrated in figure 1. Small changes in glomerular filtration rate (GFR) may produce large changes in sodium excretion. How important this is in clinical practice is unknown, as measurements of GFR are relatively crude and the factors that regulate it are not fully delineated. Similarly, the factors that control proximal tubular reabsorption of sodium are poorly defined as this segment of the nephron is not accessible to micropuncture. It is believed, however, that changes in proximal peritubular physical forces affect reabsorption at this site [11]. The argument is as follows. Anything that reduces renal blood flow (RBF) will stimulate the release of renin from the juxtaglomerular apparatus. Angiotensin II (AII) is produced within the kidney and systemically. AII acts specifically to constrict the efferent glomerular arteriole to preserve glomerular arterial pressure and to ensure that glomerular filtration continues despite reduced renal perfusion. The consequence of this preservation of glomerular filtration is an increase in the proportion of delivered plasma water that is filtered through the glomerulus. This leads to an increase in filtration fraction (FF) (FF = GFR/RBF). This is associated with a decrease in peritubular capillary blood pressure, but an increase in capillary oncotic pressure. These two factors combine to increase proximal tubular isosmotic salt and water reabsorption.

If increased proximal tubular reabsorption of sodium occurs, less solute is delivered to the thick ascending limb of the loop of Henlé (TALH). This is the only part of the nephron where sodium is reabsorbed without water—the so-called "diluting segment". Under conditions of avid proximal reabsorption of sodium, patients are unable to make a dilute urine and the administration of glucose or glucose–saline solutions is then particularly likely to produce hyponatraemia, even more so in the presence of increased plasma concentrations of the antidiuretic hormone, arginine vasopressin (AVP). In the distal nephron, further sodium is reabsorbed under the influence of aldosterone. It is clear that aldosterone is probably not solely responsible for avid reabsorption of sodium in many clinical situations, for example heart failure, cirrhosis and the nephrotic syndrome. Other mechanisms already described are probably more important for the bulk reclamation of salt and water [33].

AVP acts on the collecting duct to permit the reabsorption of water and so to regulate plasma osmolarity. During hypovolaemia the release of AVP is some 5 to 10 times greater than that seen with an increase in plasma osmolarity. The need to preserve intravascular volume, arterial pressure and perfusion of vital organs overrides the need to regulate plasma osmolarity, such that plasma concentrations of AVP are frequently increased in

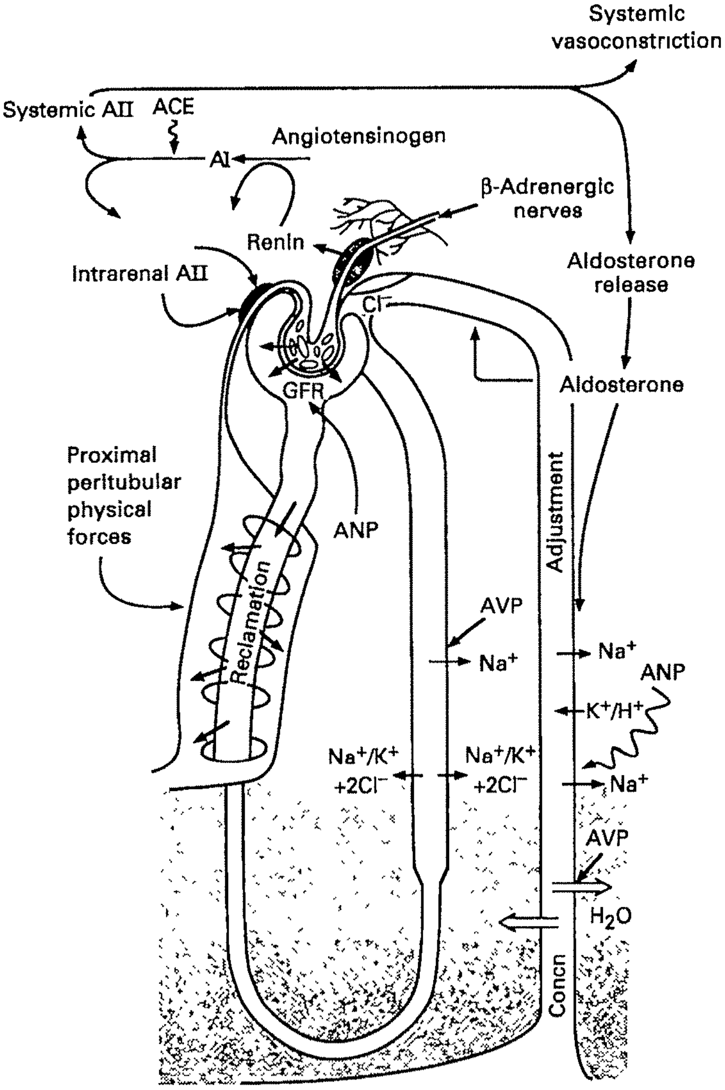

FIG. 1. Factors controlling sodium and water reabsorption. AI, AII = Angiotensins I and II; ACE = angiotensin converting enzyme; ANP = atrial natriuretic peptide; AVP = arginine vasopressin; GFR = glomerular filtration rate. Reclamation = bulk reclamation of Na^+; Adjustment = fine adjustment of Na^+ resorption; Concn = concentration. ⇝ = Inhibition.

hypovolaemic states and in heart failure, cirrhosis and the nephrotic syndrome, despite the presence of oedema and hyponatraemia. This non-osmotic release of AVP should not be considered as inappropriate. It is also important to note that AVP acts directly on TALH to promote active reabsorption of sodium [1].

The sympathetic nervous system also stimulates sodium retention by several mechanisms. Beta-adrenergic nerve fibres innervate the juxtaglomerular apparatus and stimulate the release of renin. A direct action of adrenergic sympathetic nerve fibres on tubular cells to promote sodium reabsorption has been demonstrated. The sympathetic nervous system and catecholamines also have a more subtle action, which is to produce shunting of blood from the cortex to the medulla to increase perfusion of the juxtamedullary long loop nephrons, which are adapted for avid retention of salt and water [6, 30, 32].

FACTORS RESPONSIBLE FOR STIMULATION OF SALT AND WATER RETAINING MECHANISMS

Losses

Patients frequently remain "nil by mouth" for many hours before proceeding to the operating theatre and on their return may be sedated and unable to resume oral fluids, even following minor surgery. Additional losses may occur through ventilation, vomiting, sweating and evaporation from exposed viscera during surgery. These and other factors that lead to fluid losses are summarized in table II. Many of these losses are unmeasurable. For each 1 °C increase in body temperature, losses via sweating can increase by 250 ml/24 h. With increasing age, the kidneys become less able to conserve sodium under conditions of deprivation [9]. It has been estimated that about 50 % of elderly patients going to theatre have a renal salt-losing state.

Sequestration

Fluid may be lost from the extracellular space and be unavailable to the normal economy because of sequestration within the body. Sequestration of fluid may occur in inflamed oedematous wounds, in the peritoneal cavity during peritonitis and into dilated loops of bowel during an ileus [37]. It is important to remember that with convalescence and healing this fluid may be reclaimed, and in susceptible patients can lead to acute pulmonary oedema.

TABLE II. *Fluid losses*

Preoperative	Starvation: "nil by mouth"	
	Sweating	
	Enemas	
	Diuretics	
	Vomiting: premedication	
	Nasogastric aspiration	
	Possibility of salt-losing nephropathy	
Peroperative	Blood loss	
	Evaporation:	Skin
		Exposed viscera
		Ventilation
Sequestration	Wounds: oedema from extensive dissection	
	Damaged muscles	
	Ileus	
	Ascites:	Pancreatitis
		Biliary peritonitis
		Bacterial peritonitis
	Pleural effusions	
	Generalized increased capillary permeability (lymphokines)	
	Concealed haemorrhage	

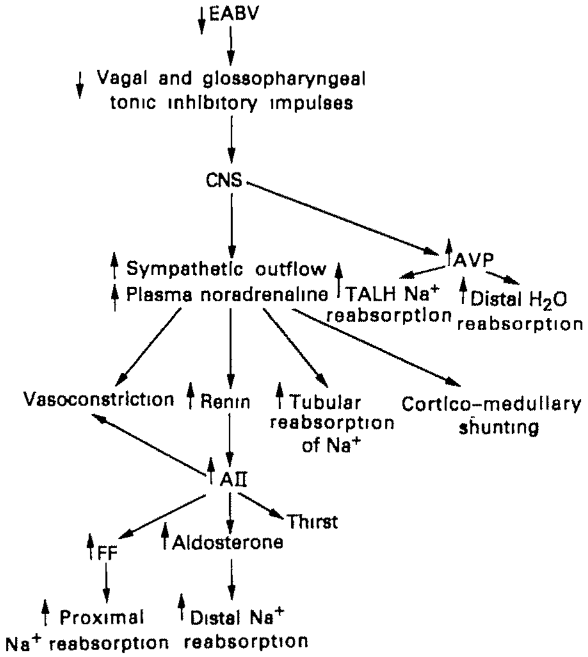

FIG. 2. Effect of reduced effective arterial blood volume (EABV). CNS = Central nervous system; AVP = arginine vasopressin; TALH = thick ascending limb of loop of Henlé; AII = angiotensin II; FF = filtration fraction.

Reduced effective arterial blood volume

The part of the blood volume that stimulates the arterial baroreceptors had been called the effective arterial blood volume (EABV) or central blood volume [29, 34]. Direct measurement is difficult, but indirect assessment is possible [14].

There are low pressure or volume receptors in the atria, particularly the left [19], and arterial or high pressure receptors in the aortic arch and carotid arteries [22]. These receptors send a stream of inhibitory impulses to the central nervous system which regulate the sympathetic nervous outflow, the release of AVP and, indirectly, the release of renin (fig. 2). Sequestration, cardiac depression, hypovolaemia from whatever cause and vasodilatation (e.g. drugs and anaesthetic agents) cause a reduction in EABV and will activate the salt and water retaining mechanisms described.

Stress

Anaesthesia and surgery are stressful pro-

TABLE III. *Haemodynamic and neurohumoral response to anaesthesia. SVR = Systemic vascular resistance; EABV = effective arterial blood volume; GFR = glomerular filtration rate; AVP = arginine vasopressin; CA = catecholamines; ACTH = adrenocorticotrophic hormone*

Vasodilatation: reduced SVR Myocardial depression	↓ EABV ↓ Renal perfusion: ↓ GFR	
Hypoxia Hypercapnia	↑ AVP, ↑ CA, ↑ ACTH	
Hypoglycaemia	↑ CA Pituitary stimulation	
Opiates	Emesis Hypotension	↑ AVP

TABLE IV. *Neurohumoral response to surgery and anaesthesia. ACTH = Adrenocorticotrophic hormone; PRA = plasma renin activity; ANP = atrial natriuretic peptide; AVP = arginine vasopressin*

Author	Year	Neurohumoral response
Hume, Bell and Bartter [16]	1962	↑ ACTH, ↑ cortisol, ↑ aldosterone
Kidd and colleagues [18]	1987	↑ Cortisol, ↑ aldosterone, ↑ PRA ↑ Adrenaline, ↑ noradrenaline ANP: no change
Moore and colleagues [26]	1955	↑ 17OH corticoids
Cline, Cole and Holden [3]	1953	↑ AVP
Cockrane [4]	1978	↑ Aldosterone
Moran and colleagues [27]	1964	↑ AVP

cedures. The neurohumoral responses have been reviewed recently [10] in relation to effector mechanisms that overlap with those that are activated by decreased EABV. Following trauma, hypovolaemia, sequestration and stress combine to produce avid retention of sodium and water [20].

Anaesthesia

Anaesthesia has systemic haemodynamic consequences (table III) which impair renal function and stimulate some of the effector mechanisms responsible for retention of salt and water [40]. Ventilation *per se* increases intrathoracic pressure and reduces venous return and cardiac output. Arterial pressure declines and blood volume is redistributed. GFR, RBF, sodium excretion and urine flow are all decreased [2].

NEUROHUMORAL RESPONSE TO ANAESTHESIA AND SURGERY

As a consequence of reduced EABV, stress, anaesthesia and ventilation, concentrations of catecholamines, AVP, renin, adrenocorticotrophic hormone (ACTH), cortisol, growth hormone (GH) and prolactin all increase, and insulin concentrations decrease (table IV). GFR declines and avid retention of salt and water occur. Intrarenal vasoconstriction occurs, with cortico–medullary shunting. Systemic vasoconstriction may occur in response to sympathetic outflow and angiotensin II, but the response may be impaired by the direct effect of anaesthetic agents.

CLINICAL EXAMINATION

Physical examination is a relatively crude means by which disturbances in salt and water balance may be detected. Pitting oedema is not detectable usually in adults until a weight gain of 5 kg occurs (i.e. 5 litre). Arterial pressure does not decrease nor the heart rate increase until there has been a 6–7 % decrease in body weight or a 10 % decrease in extracellular fluid volume. Skin turgor is increasingly unreliable with advancing age and changes are not usually detectable until body weight has declined by 4–5 %. Even measurement of central venous pressure is insensitive, with measurable changes occurring only with volume changes of 750 ml or more in the intravascular space. It is thus clear that reliance on bedside clinical observations implies that we have little idea of what changes in fluid balance are actually occurring in the perioperative period. Perhaps the most helpful investigation is that of serial body weights: no patient is too sick to be weighed. Accurate hoist scales are available (Scaletronix, 2001 sling scale, Gambro, U.K.). A sudden change in body weight of 1 kg implies a gain or loss of 1 litre of fluid.

PATTERN OF ELECTROLYTE LOSSES AFTER SURGERY

AVP concentrations are increased greatly after major surgery and may remain so for several days, and up to 1 week in some patients [20]. Renin, angiotensin and aldosterone concentrations are increased immediately after operation, but usually return to normal after 1 or 2 days as do the concentrations of catecholamines. Kidd in 1987 studied five patients undergoing cholecystectomy who were given i.v. crystalloid 3.5–4 litre [18]. He reported a three-fold increase in plasma renin activity, aldosterone, cortisol and noradrenaline and a six-fold increase in adrenaline concentrations. Interestingly, despite generous administration of i.v. fluids, there was no increase in atrial natriuretic peptide. Immediately after operation there is an inability to excrete a water load and avid retention of sodium. Although potassium is lost in the urine in the presence of increased concentrations of aldosterone, blood concentrations of potassium usually are sustained, presumably as a consequence of release from damaged tissues.

CHOICE OF I.V. FLUID

Most sodium is extracellular so that administered normal saline remains in the extracellular fluid. In the short term, normal saline will support the intravascular compartment until redistribution occurs, which may take several hours. Glucose 5% is essentially water, which is freely diffusible throughout all compartments and tissues; it is distributed through the various fluid compartments in proportion to their respective volumes. "Glucose–saline" (20% normal saline) behaves like 5% glucose. In some respects it is neither glucose (minimal calories) nor saline with regard to use for extracellular fluid volume expansion. Given routinely without thought, it is a dangerous drug and is commonly responsible for severe postoperative hyponatraemia. Theoretically, colloid solutions should remain in the intravascular compartment, but in the presence of inflammation or increased capillary permeability may actually gain access to the interstitial space. This leakage of colloid into the interstitial space is particularly worrying in the management of patients who are likely to develop the adult respiratory distress syndrome, as the administration of any fluid may increase lung water. Monitoring colloid oncotic pressure may help ensure a more appropriate use of colloid [13]. The crystalloid/colloid controversy has been reviewed by Twigley and Hillman [41]. There have been some randomized trials of colloid versus crystalloid in humans. Two studies reported no advantage to the use of colloid [23, 42]. Some reports have suggested that colloid may be harmful, increasing lung water [15] and producing a negative inotropic effect, perhaps as a result of acute reductions in ionized calcium [5]. Clearly, there are situations in which support with colloid is essential; for example, during operations on patients with ascites. If blood has been lost, the appropriate fluid for replacement is blood. Where a large volume of sequestered fluid is collecting as ascites, or as an inflammatory serosanguinous exudate, a mixture of colloid and crystalloid would be appropriate. Losses from sweating or evaporation should be made good with glucose or glucose–saline, particularly in pyrexial patients. In most instances, normal saline alternating with 5% glucose in a ratio of 1:1 or 2:1 is safe and unlikely to produce significant hyponatraemia.

ATTEMPTS TO SUPPRESS POSTOPERATIVE SALT AND WATER RETENTION

Few studies have examined adequately urine electrolytes and the plasma profiles of AVP, catecholamines and the renin–angiotensin–aldosterone system. Furthermore, no studies have compared sparing with liberal fluid provision or crystalloid with colloid. Few have included accurate daily weights in sick postoperative patients. It is not surprising, therefore, that there is great disagreement in the literature as to whether or not these neurohumoral factors can be suppressed by appropriate fluid therapy (table V). One of the better studies was that of Sinnattamby in 1974 [39], which showed that, although postoperative oliguria could be reduced and some of the hormonal factors suppressed, AVP concen-

TABLE V. *Attempts at suppression of retention of salt and water. AVP = Arginine vasopressin; CA = catecholamines; ECFV = extracellular fluid volume*

Author	Year	Attempts at suppression
Engquist and colleagues [8]	1978	Saline: Aldosterone ↓
Sinnatamby and colleagues [39]	1974	Fluids fail to suppress AVP
Zimpfer and colleagues [45]	1982	Pentobarbitone anaesthesia: CA ↓
Ecoffey, Edouard and Pruszczynski [7]	1985	Extradural anaesthesia: CA, renin, AVP ↓
Shizgal, Solomon and Gutelius [38]	1977	Saline peroperatively: Aldosterone, renin ↓
Wright and Gann [44]	1963	ECFV expansion: Free H_2O clearance ↑

trations remained increased. It does, indeed, seem likely that, with good analgesia and anaesthesia, catecholamine release may be minimized and, if adequate sodium is provided to sustain the extracellular fluid volume, renin release is minimized. AVP would appear to be more difficult to suppress. It is a primitive hormone, the structure of which is highly conserved throughout many species, implying an important physiological role. In some senses it may be considered as a haemostatic hormone essential to the defence against trauma, haemorrhage and hypovolaemia. AVP is a very potent vasoconstrictor and it is both a sodium- and water-retaining hormone. It is released in very large amounts when the EABV is reduced (the non-osmotic release of AVP). Certainly, in pharmacological quantities, AVP analogues release factor XIII–von-Willebrand complexes from the endothelium and decrease the bleeding time. It seems likely that no amount of careful manipulation of fluid is able completely to suppress the postoperative release of AVP. To administer large volumes of 5% glucose or glucose–saline as sole postoperative fluid under these circumstances is inappropriate and is frequently responsible for severe postoperative hyponatraemia.

OVER REPLACEMENT

The most common risk of excessive fluid support in the perioperative period is hyponatraemia. Since the principal physiological alteration in renal function in the postoperative period is an inability to excrete a water load as a consequence of reduced distal delivery of solute and increased concentrations of AVP (which are quite appropriate), to provide large volumes of 5 % glucose or glucose–saline as the only replacement fluid clearly is wrong. There is a widely accepted prohibition against saline for patients with advanced liver disease. Whilst it is clear that such patients will continue to accumulate ascites and oedema as long as sodium intake exceeds sodium excretion (often as little as 20 mmol day^{-1}), they too will develop rapid and often profound hyponatraemia in the postoperative period if given glucose or glucose–saline alone. Such patients need preservation of their intravascular volume with albumin and restriction of intake of both water and sodium.

Excessive fluid intake may impair gas exchange [35] and in susceptible patients may increase the risk of ARDS. Oedema *per se* is considered by some to be harmful, as it increases the distance that oxygen has to diffuse in the tissues. In the critically ill it may contribute to multiple organ failure [12]. In more normal clinical practice, this does not apply in the majority of patients who develop dependent oedema.

UNDER-REPLACEMENT

The principal risk of under-replacement is prerenal impairment, leading to established acute renal failure (acute tubular necrosis). Those who advocate a liberal approach to fluid claim a dramatic reduction in acute renal failure in postoperative and septic patients. In at-risk patients (jaundice, sepsis, the elderly) it is vital to maintain intravascular volume and good tissue perfusion and to preserve an adequate urine flow rate, but not at the price of pulmonary oedema. Monitoring central venous pressure (or in the critically ill, pulmonary capillary wedge pressure), core–peripheral temperature difference and body weight, and titrating these measurements with an appropriate fluid will prevent many cases of acute renal failure.

Other more subtle abnormalities have been reported with under-replacement in the postoperative period [17]. These include drowsiness, thirst, headaches, dizziness, malaise and delayed mobilization.

CONCLUSIONS

Preoperative deficits should be estimated and corrected as far as possible before surgery as anaesthetized patients compensate poorly for even modest deficits. Measured, unmeasured and measurable losses need to be assessed. The average 70-kg man undergoing simple surgery without fluid replacement probably loses about 1 litre of fluid. For major surgery, particularly in pyrexial patients, losses and sequestration can be very great. Careful monitoring is necessary to guide fluid replacement. It is important that this fluid replacement is provided early to limit activation of the neurohumoral mechanisms responsible for salt and water retention. Fixed regimens are dangerous in sick patients. The perioperative requirement for saline may range between 0.5 and 3 litre, depending on the type and duration of surgery in addition to an allowance being made for actual measured losses. Postoperative oliguria may not be completely avoidable, but postoperative acute renal failure certainly should be. Fluid replacement needs to be appropriate to the type of fluid lost (table VI) and must recognize the marked inability of postoperative patients to excrete a water load. Losses of predominantly water (such as by sweating and evaporation) do occur but are uncommon and require replacement with 5% glucose. Gastrointestinal losses usually contain less sodium than is in normal saline and alternating 5% glucose and normal saline is usually a safe adequate replacement. Blood and protein losses should be replaced with blood and colloid solutions, respectively.

TABLE VI. *Appropriate fluid replacement*

Loss	Replacement
Sweating Evaporation	5% Glucose
Diarrhoea	Alternating 5% glucose/normal saline or glucose–saline
Upper gastrointestinal tract losses	Chloride (as above) and K^+ (H^+ as HCl in severe cases)
Burns Peritonitis Crush injury	Albumin
Haemorrhage	Blood
Ileus	Normal saline

Oliguria does not develop in perioperative patients as a result of acute frusemide deficiency. Diuretics do not improve GFR. Patients should be euvolaemic, with free drainage of urine ensured before i.v. diuretics are administered to provoke a diuresis. Simply "pushing fluids" in the hope that the kidney will respond to an increase in atrial natriuretic hormone is too simple and may lead to acute pulmonary oedema. As in all things, not enough is just as bad as too much.

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MANAGEMENT OF HYPONATRAEMIA

J. D. SWALES

A reduction in the serum concentration of sodium is one of the commonest biochemical abnormalities in hospital inpatients. In most cases it should be regarded as an incidental finding which will be corrected with treatment of the underlying condition. In certain situations, however, it can produce severe life-threatening neurological disease. Evidence has also been produced that in some situations ill-advised treatment can induce equally severe neurological disease. Management therefore demands an understanding of the causes and pathophysiology of hyponatraemia.

Pseudo-hyponatraemia

An apparent decrease in serum sodium concentration (measured by flame photometry) occurs when the mass of the non-aqueous components of serum is increased in severe hyperlipidaemia and hyperproteinaemia [40]. Pseudohyponatraemia can be identified readily by measurement of serum osmolality, which will be normal under these circumstances.

CAUSES OF HYPONATRAEMIA [15, 37]

Hyponatraemia is the result of alteration in one of the determinants of the serum concentration of sodium:

(a) Total quantity of metabolically active sodium, usually estimated as the total exchangeable sodium. Total body concentration of sodium assessed, for instance, by neutron activation analysis, measures bound sodium contained predominantly in bone.

(b) Total quantity of metabolically active potassium, estimated as total exchangeable potassium, which is almost equal to total body potassium. Since potassium is largely an intracellular cation, whole body potassium determines the distribution of water between the extra- and intracellular compartments.

(c) Total body water.

(d) Factors other than sodium–potassium which may, in certain clinical situations, change the ratio between intracellular and extracellular water. Thus glucose and mannitol increase serum osmolality and so tend to remove water from the cells and dilute the sodium contained in extracellular fluid and serum [33]. The intracellular release of organic molecules following electroconvulsive therapy may cause a transient movement of fluid into the cells with the development, for instance, of hypernatraemia [41].

The complexity of the determinants of serum concentration of sodium implies that there is no clinical value which can be placed upon a single measurement of this variable considered in isolation. It can be interpreted only in the light of clinical information.

The causes of hyponatraemia are manifold, but attributable to the mechanisms shown in table I.

Redistribution of water. Hyponatraemia as the result of potassium depletion (with movement of water from the cells into the extracellular space) or as a result of extracellular solute load (e.g. after infusion of mannitol) rarely, if ever, causes problems in its own right.

Hyponatraemia as a result of water retention. On a normal diet, a healthy adult may excrete as much urine as 22 ml min^{-1} [32]. Excessive water intake rarely causes significant hyponatraemia, therefore, in the presence of good renal function. Most patients with this problem have been psychotic, compulsive water drinkers whose solute intake and therefore, probably, diuretic capacity was probably more limited [10, 26].

KEY WORDS
Acid–base equilibrium. sodium. Ions. sodium

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TABLE I. *Mechanisms of hyponatraemia*

- (1) Decreased free water clearance caused by ADH
  - Administration of vasopressin or its analogues
  - Inappropriate secretion of ADH (malignant neoplasms, central nervous system lesions, pulmonary tuberculosis, pneumonia and IPPV)
  - Appropriate secretion in response to extracellular fluid volume contraction
  - Secretion in response to "effective extracellular volume contraction" (e.g. congestive cardiac failure, cirrhosis and nephrotic syndrome)
  - Secretion in response to increased sympathetic nervous system activity
  - Baroreceptor stimulation
  - "Stress"
- (2) Decreased free water clearance caused by other agents (e.g. oxytocin, diuretics)
- (3) Retention of water caused by renal disease
- (4) Decreased free water clearance caused by local reversible renal causes
  - Decreased delivery of solute load to diluting segment as a result of decreased renal blood flow and glomerular filtration rate and increased proximal tubular sodium reabsorption
  - Change in water permeability of loop of Henlé and collecting ducts not caused by ADH (e.g. steroid deficit)
- (5) Movement of water from intra- to extracellular compartments
  - Potassium depletion
  - Infusions (e.g. mannitol and dextran)
  - Hyperglycaemia

Water overload is much more frequently the result of impaired renal mechanisms of water excretion. This may occur in chronic renal failure or in the presence of hormones or drugs which reduce free water clearance. Antidiuretic hormone (ADH) may be secreted not only in response to water depletion, but also in response to decreased extracellular fluid volume. Thus sodium depletion as a result, for instance, of gastrointestinal sodium losses, may be associated with hyponatraemia secondary to ADH-induced water retention. Vasopressin concentrations are increased also in conditions such as congestive cardiac failure or cirrhosis of the liver, as a result of decreased effective extracellular fluid volume. Hyponatraemia is the rule rather than the exception in these conditions. Vasopressin concentrations are increased also as a result of surgical operations. Hypovolaemia may play a role, but increased sympathetic efferent activity is probably more important [3, 17].

Decreased renal blood flow as a result of major surgery may add further impairment to free water clearance. As a result the body's major protective mechanism against water retention is impaired, making the risks of infusion of excessive quantities of fluids containing small concentrations of sodium particularly great. Continuous irrigation of the bladder with hypotonic solutions of glycine following transurethral prostatectomy constitutes a special case in which large volumes of hypotonic fluid may be absorbed during and after the operative procedure. Hyponatraemia is a frequent complication of this procedure [19].

Water retention and hyponatraemia can also be the result of the administration of drugs [37]. Oxytocin, the antidiabetic sulphonylurea compounds (particularly chlorpropamide), clofibrate, the diguanides, carbamazepine, cyclophosphamide, vincristine, and non-steroidal inflammatory drugs all may impair the renal capacity to excrete water either directly or indirectly through vasopressin. Diuretic therapy with either thiazide or loop diuretics is frequently associated with hyponatraemia [16]. Three mechanisms theoretically contribute: direct interference of the diuretic with free water clearance; sodium depletion stimulating water retention through the secretion of vasopressin and potassium depletion.

The postoperative patient is at particular risk of hyponatraemia, therefore, since his capacity for free water clearance may be impaired by the physiological response to the stress of surgery and perhaps compounded by preoperative drug therapy (such as with thiazide diuretics) or by coexistent renal disease.

PATHOPHYSIOLOGY

The initial reduction in the serum concentration of sodium creates an osmotic gradient across the plasma membrane between the intra- and extracellular fluid. As a consequence, cellular oedema occurs. Whilst this is a general phenomenon, it assumes clinical significance in the case of the brain, which occupies a closed compartment [5, 20]. Such osmotically-induced brain oedema is predictably associated with rapid decreases in serum sodium concentration, usually caused by the administration of water or hypotonic fluids either therapeutically or as a result of accident or mental disturbance.

Intracellular osmolality is reduced by the influx of water, but then a further adaptation occurs. Intracellular, osmotically active solutes are reduced through the loss of intracellular ions [5, 20] and amino acids (particularly taurine) [38]. The lost cations are predominantly potassium, with lesser quantities of sodium; the major anion is chloride. The mechanism appears to be through activation of ouabain-resistant transmembrane channels. As a result, cellular oedema is limited in chronic hyponatraemia as a new steady state is reached in which both intra- and extracellular osmolality is reduced. In studies of the hyponatraemic rabbit, for instance, brain water was increased by 19% at 12 h, but only by 7% at 3.5 days [20]. If serum osmolality is acutely restored to normal values, therefore, a reverse osmotic gradient will be created between cells and serum, giving rise to cell shrinkage. Such acute restoration of serum sodium to normal or hypernatraemic concentrations has been associated with the syndrome of central pontine myelinolysis [13, 29, 39]. The relationship of this syndrome to rapid correction and to neurological deterioration during the treatment of hyponatraemic patients is a source of unresolved controversy. Central pontine myelinolysis was described first in 1959 [1]. It was shown subsequently to be associated with extrapontine lesions affecting the thalamus, internal capsule, cerebellum, lower levels of cerebral cortex and adjacent white matter [29]. The earlier clinical observations associated it with malnutrition and chronic alcoholism, but it was later recognized in hyponatraemic patients [29]. It was then shown that, in the dog [28], rat [25] and rabbit [23], central pontine myelinolysis could be induced by rapid correction of hyponatraemia. The extent of the change in serum sodium required to induce the lesion is debated. Restoration of serum sodium to normal concentrations undoubtedly generates the lesion [8]. Restoration to mildly hyponatraemic values (according to some groups) is also potentially harmful in experimental hyponatraemic models [34]. Chronicity of hyponatraemia also appears to be a factor which predisposes to lesions when correction is rapid [30].

In addition to cerebral oedema and central pontine myelinolysis, it has been claimed that there is a third type of lesion in hyponatraemic patients. Two to 3 days after recovering from coma, some patients have suffered grand mal seizure and irreversible coma [4]. This biphasic illness bears a resemblance to delayed anoxic encephalopathy following cardiac arrest, carbon monoxide intoxication or aspiration [31] and it has been suggested, therefore, that the neurological lesion in hyponatraemia has a similar pathological basis. In anoxic encephalopathy the underlying lesion is one of diffuse cerebral demyelination [11]. Laureno and Karp have pointed, however, to the differences between the biphasic course of hyponatraemic neurological disease and the biphasic course of anoxic encephalopathy [29]. The latter occurs much later (between 1 and 4 weeks) and has a much more gradual mode of onset. When it occurs, they suggest that the second episode of neurological deficit is the result of central pontine myelinolysis. Although this lesion could not be demonstrated in the largest group of patients with a biphasic course [4], it was not sought specifically and could not, therefore, be excluded by the author. An alternative explanation which he put forward was of brain stem herniation, of which there was evidence in three of his patients, in the form of uncal grooving and compression at autopsy [4].

RAPID OR SLOW CORRECTION OF HYPONATRAEMIA?

In both man and experimental animals, it has long been recognized that an acute increase in the serum concentration of sodium produces neurological deficits which have been attributed to acute changes in brain volume and subsequent haemorrhage [18]. Likewise, rapid correction of hypernatraemia by hypotonic fluid infusions produces neurological lesions [12]. The circumstances under which an acute increase in serum sodium from hyponatraemic concentrations may be dangerous have caused considerable discussion and controversy over the past few years. The difficulty has lain in the distinction between neurological injury occurring as a result of hyponatraemia or the condition which gave rise to hyponatraemia on the one hand, and neurological disease resulting from the rapid increase in the serum concentration of sodium on the other.

Several case series pointed to the benefits of rapid correction of hyponatraemia with hypertonic saline solutions, often combined with diuretics, where overload with low sodium-containing infusions had played a role in pathogenesis [6, 7, 9]. Neurological injury, where it occurred, was attributed to the hyponatraemia and possible delays in treatment [7]. Rapid correction at the approximate rate of 2 mmol $litre^{-1}$ h^{-1} increase in serum sodium concentration was recommended on these grounds. In contrast, the experimental data demonstrate unequivocally that rapid correction of sustained hyponatraemia produces central pontine myelinolysis [23, 25, 28]. Several clinical reports link this lesion with rapid correction in hyponatraemic man [13, 29, 35, 36, 39]. The difficulty in proving cause and effect in man is formidible. Severe hyponatraemia giving rise to permanent neurological damage is relatively rare. Each individual case varies in predisposing factors, timing and severity of electrolyte disturbances, associated diseases and frequently, documentation. It is most likely, for instance, that patients with the most severe metabolic disturbance are selected for the most aggressive therapy, and hence spurious associations between therapy and adverse effects may be created.

In an attempt to resolve these issues, several more systematic reviews of the clinical course of hyponatraemic patients have been published in the past few years. Sterns, Riggs and Schochet reported eight patients who developed a clinical syndrome with findings typical of central pontine myelinolysis following correction of severe hyponatraemia at a rate greater than sodium 12 mmol litre^{-1} day^{-1} [36]. Although the clinical findings were regarded as characteristic, the diagnosis was confirmed only by autopsy on two patients and by CT scan on the third. Five of the eight patients had been treated at one of the participating hospitals and a retrospective case review showed 60 patients with serum concentrations of sodium less than 116 mmol litre^{-1} over a 5-yr period. No patient whose serum concentration of sodium had been increased by less than 12 mmol litre^{-1} day^{-1} had shown neurological sequelae. Sterns' group proceeded to carry out a literature review of the outcome in 80 patients who presented with serum sodium concentrations less than 106 mmol litre^{-1} [36]. Of the 51 in whom documentation was adequate, more than 50% had undergone "rapid correction" of serum sodium; 14 of these had documented or suspected central pontine myelinolysis and clinical data on two others strongly suggested the diagnosis. These were contrasted with 13 patients in whom the correction rate was less than 12 mmol litre^{-1} day^{-1}, who recovered without complications. Their conclusion was "patients who present with chronic hyponatraemia should be treated conservatively—(primarily with water restriction and withdrawal of thiazide diuretics). We hope that in this way the osmotic demyelination syndrome, a disease we fear that is now too common, will fade into obscurity". In assessing the relevance of this paper, it is important to note that the authors attributed hyponatraemia to diuretic therapy in seven of the eight patients who presented with neurological damage and to diarrhoea in the eighth. Serum sodium was also recorded as increasing to hypernatraemic concentrations in two patients (156 and 146 mmol litre^{-1}). Five of the patients were aged 60 yr or more and the youngest was 41 yr. The patients at risk in this study, therefore, appeared to be older patients with probably chronic hyponatraemia. A further later report from the same group [35] described experience with 64 episodes of severe hyponatraemia (serum sodium concentrations of 110 mmol litre^{-1} or less). All these patients were symptomatic, although the severity of symptoms was much greater in patients with acute hyponatraemia, of whom 70% were unresponsive when first diagnosed. Thirty percent were known to have seizures. In contrast, only 17% of patients with chronic hyponatraemia were unresponsive and only 7% of these had had seizures. Most patients with chronic hyponatraemia were conscious on presentation, but showed lethargy, confusion, disorientation, dysarthria and gait disturbance. Only one death was attributed to neurological injury (central pontine myelinolysis). Four other patients died of underlying disease. Serum sodium concentration was corrected rapidly in only 6% of the patients and in 50% of these the rapid rate of correction was the result of spontaneous water diuresis. Only one of the cases of chronic hyponatraemia was corrected rapidly—the patient who developed central pontine myelinolysis. The authors concluded that, even in severe hyponatraemia presenting with neurological disturbance, the prognosis is relatively good and therefore that delay in correction carries little risk. As in the previous report, the number of patients with acute hyponatraemia secondary to fluid overload was small (10 patients in all). It was attributed to the administration of parenteral fluids and the syndrome of inappropriate secretion of ADH in five patients, to psychotic polydipsia in four patients and Addison's disease in one.

By contrast Ayus, Olivero and Frommer [9] described seven patients with very low serum concentrations of sodium who made an uncomplicated recovery after rapid correction of hyponatraemia using 3% hypertonic saline solution (average increase in serum concentration of sodium, 2.4 mmol litre^{-1} h^{-1}). Hyponatraemia was attributed to fluid overload in four of the

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ROLES OF THE LIVER AND KIDNEY IN ACID–BASE REGULATION AND ITS DISORDERS

R. D. COHEN

The past 15 years have produced some surprising reinterpretations of the mechanisms of acid–base regulation and of the biochemical pathogenesis of metabolic acid–base disorders. Several well established concepts have been questioned, with possible eventual consequences for clinical management. The purpose of this review is to summarize some of this newer thinking and its implications.

Probably the best starting point is the Henderson–Hasselbalch equation itself. Many textbooks have inferred from it that acid–base homeostasis can be regarded in simple terms as a joint function of the lungs and kidneys, the former controlling $P\text{CO}_2$, the latter plasma [HCO_3^-], thus ensuring constancy of arterial pH. The rethinking has been centred largely around the possible role of the liver in both acid–base homeostasis and its disorders, and reappraisal of the role of the kidneys, which appear to have a subtler role than the mere excretion of buffered protons.

METABOLIC PRODUCTION AND CONSUMPTION OF PROTONS

A resting adult in a steady state produces total lactate of about 1300 mmol day^{-1} and the same amount of protons from peripheral tissues, mainly skin, gut, skeletal muscle, brain and erythrocytes. The protons titrate local blood and tissue bicarbonate. The lactate ions are removed, principally by the liver, but also by the kidneys and heart. The principal disposal pathways are gluconeogenesis (the main route in the liver) and oxidation to carbon dioxide and water. As may be seen in the following equations, whichever route of lactate disposal is followed, one proton (H^+) is consumed per lactate ion metabolized:

$$\underset{\text{lactate}}{2CH_3CHOHCOO^-} + 2H^+ \rightarrow \underset{\text{glucose}}{C_6H_{12}O_6}$$

(gluconeogenesis)

$$CH_3CHOHCOO^- + H^+ + 3O_2 \rightarrow 3CO_2 + 3H_2O$$

(oxidation)

The consumption of a proton effectively means the regeneration of a bicarbonate ion, as follows:

$$\begin{tikzcd} 2H_2O \rightarrow 2H^+ + 2OH^- \arrow[d] \\ 2OH^- + 2CO_2 \rightarrow 2HCO_3^- \end{tikzcd}$$

(Protons used in lactate oxidation or gluconeogenesis are derived in this way.)

This bicarbonate, produced largely in the liver, then replaces that lost at the periphery by the titration alluded to above. Acid–base homeostasis is maintained in this way normally. Since the liver has such a large role in this cycle, it is clearly possible that disruption of hepatic metabolism of lactate could be responsible for metabolic acidosis. Furthermore, it must be asked whether there is any direct feedback control of hepatic metabolism of lactate in a sense which would counteract any tendency to acidosis or alkalosis.

Similar questions need to be asked about urea synthesis by the liver, for reasons which have been pointed out by Oliver and Bourke [32], Atkinson

KEY WORDS

Acid–base equilibrium: metabolic acidosis, respiratory acidosis, pH Liver: metabolism. Kidney: function, urine.

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and Camien [5] and Atkinson and Bourke [3, 4]. A simple way of writing the overall equation for urea synthesis in the liver is as follows:

$$CO_2+\underset{\text{ammonium}}{2NH_4^+}\rightarrow\underset{\text{urea}}{CO(NH_2)_2}+H_2O+2H^+$$

Thus for every mol of urea synthesized, 2 mol of H^+ is produced, and on a protein diet averaging 100 g day^{-1} this amounts to the enormous quantity of about H^+ 1000 mmol day^{-1}. It was Atkinson and Camien [5] who drew attention to the fate of most of this H^+. They pointed out that, when proteins are broken down to amino acids and subsequently deaminated before oxidation of the carbon skeletons to carbon dioxide and water, bicarbonate 1 mol is produced per mol of "neutral" amino acid oxidized. (A neutral amino acid is one which contains one carboxylate and one amino group.) The complete oxidation of the carbon skeletons of the amino acids from 100 g of a hypothetical protein which contained only neutral amino acids would produce about 1000 mmol of bicarbonate—which, if it remained un-neutralized, would have to be excreted by the kidneys to prevent alkalosis. This obviously does not happen, and Atkinson and Camien proposed that a principal function of urea synthesis was to provide the protons to neutralize this bicarbonate. The NH_4^+ used for urea synthesis is, of course, the deamination product of the same amino acids, but NH_4^+ is too weak a proton donor (too weak an acid) to donate protons directly to HCO_3^-. The liver uses energy in the form of ATP to drive synthesis of urea from NH_4^+ and in the process produces the necessary H^+ for the neutralization of bicarbonate. In the hypothetical situation of a protein containing only neutral amino acids, if all the amino groups were utilized in the production of urea, the protons produced would neutralize exactly the HCO_3^- formed during the oxidation of the carbon skeletons.

The situation is complicated only slightly by the fact that proteins do not contain neutral amino acids alone. Dicarboxylic amino acids such as glutamate and aspartate will, on deamination and oxidation, produce two HCO_3^- and one NH_4^+; in contrast, basic amino acids such as lysine will produce two NH_4^+ per HCO_3^- and metabolism of the sulphur of sulphur-containing amino acids will produce two protons per atom of sulphur oxidized to sulphate. So the extent to which the HCO_3^- is under- or over-neutralized by urea synthesis depends on the relative amounts of these special categories of amino acids in the protein mix being oxidized *and* on the proportion of the amino nitrogen which the liver converts to urea—a question to which we will return. As in the case of the involvement of the liver in lactate metabolism, two questions have to be asked. First, is urea synthesis regulated in a manner homeostatic for acid–base regulation, and second, if so, can this homeostatic system be overridden or disturbed in ways which give rise to acid–base disorders?

The liver is the sole source of production of ketoacids, in relatively small concentrations in the well fed state, but much increased in starvation and particularly in diabetic ketoacidosis. It is generally held that the liver is the source of the protons causing the acidosis in ketoacidosis. It will be seen later that this may partly or wholly be an illusion, and that in fact the ketoacidotic state represents a rather remarkable perturbation of the role of the liver in acid–base homeostasis.

NITROGEN DISPOSAL BY THE LIVER AND KIDNEYS IN RELATION TO ACID–BASE REGULATION

Physiology

The conventional view of the role of the kidney in acid–base homeostasis is that protons are excreted buffered by either phosphate:

$$HPO_4^{2-}+H^+\rightarrow H_2PO_4^{1-}$$

or ammonia:

$$NH_3+H^+\rightarrow NH_4^+$$

Typically, H^+ 75–100 mmol day^{-1} may be excreted this way, 65–75% as NH_4^+. During acidosis the phosphate buffer is titrated more fully (it is 50% titrated at pH 6.8 and virtually fully titrated at pH 5) and the rate of excretion of ammonia is increased up to 5–10 times normal, so that a similarly increased rate of excretion of protons buffered as NH_4^+ occurs. The daily rate of urinary acid excretion may therefore be calculated as the following sum of excretion rates:

$$(\text{titratable acidity}+NH_4^+-HCO_3^-)$$

Here, titratable acidity represents the acid buffered by phosphate. HCO_3^- is virtually absent from the urine at pH 6.0.

These conventional views were severely challenged when Oliver and Bourke [32] pointed out that they contained a physicochemical error, as follows. Urinary NH_4^+ is derived from the enzymic hydrolysis of glutamine. The equation of hydrolysis is customarily written:

$$\underset{\text{glutamine}}{CONH_2(CH_2)_3CHNH_2COOH} + H_2O \rightarrow \underset{\text{glutamate}}{COOH(CH_2)_3CHNH_2COOH} + NH_3$$

but if the equation is written more correctly with these changes present at prevailing pH, we have:

$$CONH_2(CH_2)_3CHNH_3{}^+COO^- + H_2O \rightarrow COO^-(CH_2)_3CHNH_3{}^+COO^- + NH_4{}^+$$

In this second equation $NH_4{}^+$ appears, not NH_3. Since, at the moment of generation, the "ammonia" is really ammonium, it already has a proton attached and cannot buffer further protons. It follows that in the calculation of the daily excretion of buffered protons, the term $NH_4{}^+$ must be deleted. Furthermore, the 5–10 fold increase in $NH_4{}^+$ excretion during severe acidosis cannot represent an effort by the kidneys directly to excrete more protons.

This argument has raised considerable discussion [18, 39], directed principally towards its implications rather than its validity. An immediate teleological question which arises is as to the purpose of $NH_4{}^+$ excretion and its increase in acidosis if not to buffer protons. Atkinson and Bourke and their colleagues [3–5, 32] have pointed out that the increased excretion of $NH_4{}^+$ in acidosis deprives the liver of what otherwise would be substrate for urea synthesis and concomitant proton production. There is therefore *less neutralization* of $HCO_3{}^-$ produced from the metabolism of the carbon skeletons of amino acids and in this way increased urinary excretion of $NH_4{}^+$ counteracts the acidosis. Atkinson and Camien [5] suggested that it is incorrect to regard renal secretion of $NH_4{}^+$ as being designed as a vehicle of H^+ excretion; rather, acidification of the urine is designed to increase excretion of $NH_4{}^+$ and therefore decrease formation of urea. We therefore begin to redefine the role of the kidney in acid–base homeostasis. Rather than acting as a direct proton excretor, it acts as a "sorting house", dictating the route of nitrogen disposal: either to the liver for urea synthesis and H^+ production, or to the urine as $NH_4{}^+$, which has no "proton penalty".

There have been two main criticisms of this view. The first is that, when glutamine is converted into glutamate and then 2-oxoglutarate during the renal production of $NH_4{}^+$, metabolism of the oxoglutarate generates one $HCO_3{}^-$ for each $NH_4{}^+$, and the process is therefore stoichiometrically equivalent to H^+ excretion. Häussinger, Gerok and Sies [22] have pointed out, however, that the oxoglutarate thus produced merely replaced oxoglutarate which was substrate for the original formation of the glutamine used as a transporter of nitrogen to the kidney. Since protons were released originally during the production of the original oxoglutarate, the bicarbonate generated by the metabolism of renally generated oxoglutarate merely neutralizes these protons, with no overall implication for acid–base balance. The other view often taken is that, because 1 mol of $NH_4{}^+$ excreted in the kidney thereby prevents the liver forming urea 0.5 mol and proton 1 mol, this is stoichiometrically equivalent to saying that for each 1 mol of $NH_4{}^+$ excreted, H^+ 1 mol has been eliminated; therefore, urinary $NH_4{}^+$ excretion is still a quantitative measure of H^+ elimination. This is incorrect, for an important reason: it assumes that every time the kidney excretes an extra $NH_4{}^+$ 1 mol, hepatic production of urea is decreased by precisely 0.5 mol. There is, however, no evidence that (in the short term at least) the liver behaves quantitatively in this "slavelike" fashion. There are, in fact, many other influences on the synthesis of urea besides substrate supply; these include hormones such as glucagon [37] and vasopressin [15, 37], the state of nutrition [36] and, as we shall see, the acid–base status itself. Thus a failure of homeostasis could arise from the liver failing to react *promptly and stoichiometrically* in terms of urea synthesis to variations in nitrogen supply dictated by the renal response to an acid–base disturbance.

It is clear, however, notably from the work of Häussinger and his colleagues [20, 21, 23] that there is, in addition, a potential mechanism *intrinsic to the liver* for regulating the pathways of nitrogen disposal in the interests of acid–base balance. Häussinger's group and others demonstrated that urea synthesis—mainly from $NH_4{}^+$ and glutamine—is located mainly in the periportal cells of the sinusoid, whereas glutamine synthesis (another route of $NH_4{}^+$ disposal) is strictly confined to the last one or two cells in the sinusoid (i.e. those close to the centrilobular vein), which are the only cells containing the enzyme glutamine synthetase (fig. 1). The mechanism of synthesis of urea in the periportal cells is as follows. The prime substrates for the initial and rate limiting

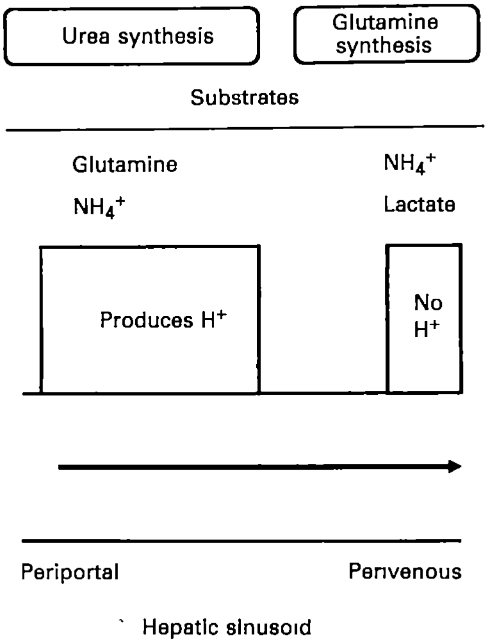

FIG 1. Organization of nitrogen disposal mechanisms along the hepatic sinusoid. Synthesis of urea occurs at the periportal end and is accompanied by proton production. Glutamine *breakdown* contributes to the NH_4^+ needed for synthesis of urea. Glutamine *synthesis* occurs in the final cells of the sinusoid, close to the centrilobular vein and is unaccompanied by changes in proton balance. Overall net glutamine balance across the liver is the sum of these two processes.

reaction (the formation of carbamyl phosphate) are bicarbonate, ammonia (NH_3) and ATP and, for the purposes of urea synthesis, this reaction takes place in the mitochondria. The HCO_3^- is derived locally, some of it through a special mitochondrial isoenzyme of carbonic anhydrase. The NH_3 comes from NH_4^+ supplied by the blood, by the action of a specific hepatic glutaminase on glutamine (which again reaches the liver via the circulation) and by oxidative deamination of glutamate, derived both from blood and locally. There is now substantial evidence that synthesis of urea, both from NH_3 and from glutamine, is inhibited by decreasing blood pH within the clinically relevant pathophysiological range. A number of mechanisms contribute to this, including: decreased gradient of NH_3 across the plasma membrane as a result of changes in the pH gradient [8], decreased transport of glutamine into the hepatic mitochondria [26], decreased activation of glutaminase by NH_4^+ [38] and diminished supply of HCO_3^- [21].

Häussinger has suggested that NH_4^+ which failed to be converted periportally into urea because of the acidotic inhibition mechanisms described above, would pass down the sinusoid and be "scavenged" by the glutamine synthesizing cells, which thus convert the escaping NH_4^+ into glutamine rather than urea. A switch from net uptake of glutamine by the liver in normal acid–base conditions to net output in acidosis is well established [2, 20, 28]. Häussinger pointed out that the advantage of such a switch for acid–base homeostasis could be that glutamine synthesis as a route of disposal of NH_4^+ carries no penalty of proton production, in contrast to disposal by synthesis of urea [23].

Almond and colleagues have examined two aspects of Häussinger's hypothesis [2]. First, its validity depends on the nature of the carbon substrate for synthesis of glutamine. The two most likely are glucose and lactate; it can be shown that if lactate is the substrate, glutamine synthesis is free of the penalty of proton production, but this is not the case if the substrate were glucose. We have shown in perfused rat liver that lactate is indeed the preferred substrate [Almond and colleagues, unpublished observations]. However, although we have confirmed a linear decrease in the rate of synthesis of urea as perfusate pH decreased from 7.4 to 7.0 [2], the rate of glutamine synthesis did not vary at all with pH; the change from negative to positive glutamine balance across the liver in acidosis is attributable entirely to inhibition of urea synthesis. The consequence is that increased quantities of NH_4^+ leave the liver in acidosis, scavenging by the centrilobular cells having been inefficient. The possibility was considered that an increase in glutamine synthesizing capacity would be seen only in livers from chronically acidotic animals, but the data did not support this suggestion. We were therefore unable to support Häussinger's hypothesis in its complete form, although it is possible that it might be valid *in vivo*, but not under the conditions selected in our isolated perfused liver studies. However, the essential feature of Häussinger's hypothesis is that acidosis switches disposal of NH_4^+ from a proton-producing to a proton-neutral route. It does not in fact matter what the proton-neutral route is, and it is clear that, if the NH_4^+ rejected for urea synthesis were simply excreted as NH_4^+ in the urine, this would suffice. We have demonstrated [unpublished] that during the development of uraemic acidosis in bilaterally nephrectomized rats there is a marked increase in blood [NH_4^+], consistent with this suggestion, although not proving it.

Another unexplored possibility for a short-term site of storage of NH_4^+ is bone.

Clinical implications of hepatic switching of nitrogen disposal routes in acid–base disorders

The reappraisal of acid–base regulation in respect of disposal of nitrogen outlined above leads to possible reinterpretations of the pathogenesis of many metabolic acid–base disorders; a few examples are given here.

Liver disease. A substantial proportion of patients with fulminant hepatic failure, whose acid–base status is documented before the onset of circulatory failure, exhibit *metabolic* alkalosis, rather than the more familiar respiratory alkalosis [35]. When these observations were made in 1975 their explanation was not apparent. It now seems possible that the failing liver does not produce sufficient urea, with accompanying protons, to neutralize the bicarbonate produced from amino acid carbon skeletons being oxidized in increased quantities as part of the catabolic state. This suggestion conforms with the findings reported in an important recent paper from Häussinger's group [24] in which, in a group of patients with cirrhosis or fatty liver, the plasma concentration of bicarbonate was shown to be inversely related to the hepatic capacity for urea synthesis. Even more strikingly, urinary NH_4^+ excretion in these patients was *positively* related to plasma pH and bicarbonate concentration; this is opposite to the usual negative relationship, and suggests that renal excretion of NH_4^+ is a mechanism for excreting that nitrogen which cannot be incorporated into urea in the liver, rather than a mechanism subserving acid–base regulation, as is considered conventionally [19].

Uraemic acidosis. The classical explanation of the acidosis of renal failure is based on the observation of decreased urinary excretion of NH_4^+ in this condition. This was considered to represent a failure of excretion of buffered protons, an interpretation which can no longer be sustained in view of the arguments outlined. A more probable explanation [5] is that nitrogen which has failed to be excreted by the kidneys as NH_4^+ has been converted to urea by the liver, and the accompanying production of protons is responsible for the acidosis. This implies that the acidosis of renal failure is the result of overproduction, as opposed to underexcretion, of protons. It would require production of urea to increase by only a tiny percentage to result eventually in uraemic acidosis and this increase in production might not be detected by conventional means. It may be asked why the intrinsic hepatic mechanism of inhibiting production of urea in acidosis does not prevent the development of acidosis. The answer to this may be that few biological feedback systems have 100% gain, and acidotic inhibition of ureogenesis may be overcome partly by substrate pressure. These suggestions are clearly susceptible to experimental evaluation.

Compensation for respiratory acidosis. A sudden increase in P_{CO_2}, caused for example by an exacerbation of chronic obstructive airways disease, causes a decreased arterial pH followed by an increase towards normal over the next few days as a compensatory increase in plasma concentration of bicarbonate occurs. The usual explanation of the increase in plasma HCO_3^- is that the increased P_{CO_2} has stimulated the renal reabsorption of bicarbonate. There is, however, some doubt as to whether this explanation is quantitatively sustainable, for the following reasons. Suppose that the patient has an initial urinary pH of 6.5. At this value, urinary excretion of bicarbonate is very small indeed. Proton secretion has to be buffered since the urine pH cannot decrease to less than 4.5. We have seen that the NH_3–NH_4^+ system can no longer be considered as the buffer, so increases in urinary content of NH_4^+ are not relevant. The only buffer system of any magnitude remaining is the phosphate system, which may be responsible under ordinary conditions for excretion of about 30 mmol day^{-1} of buffered protons. At pH 6.5, 75% of the phosphate system is already in the protonated form, so only about 7–8 mmol day^{-1} of extra H^+ can be excreted as $H_2PO_4^-$, and this represents the increased amount of HCO_3^- which is generated by the kidneys. In 4 days this amounts to 30 mmol which, even in the unlikely event of it remaining entirely in the extracellular compartment (say 14 litre), would result in an increase of only 2 mmol of plasma bicarbonate in 4 days; this may not be enough to account for the observed increase, even when the direct physicochemical effect on bicarbonate of increasing P_{CO_2} has been taken into account. Another source of bicarbonate has to be sought, and this could be provided by inhibition of synthesis of urea by respiratory acidosis [33], with consequent failure to neutralize amino acid-derived bicarbonate. It should be noted that, the greater the initial urinary pH, the less necessary is this alternative route. Again, experimental testing of these suggestions is required.

Therapeutic implications. The obvious possibility is manipulation of acid–base balances by drugs which alter urea synthesis directly. We are unaware of any current suitable agent. One of the clear requirements of a strategy which inhibits synthesis of urea in order to control metabolic acidosis is that blood NH_4^+ does not increase sufficiently to produce ammonia intoxication. Demonstrations of the adaptability of the renal route of elimination of NH_4^+ to nitrogen elimination rather than acid–base regulation [5, 24] provide some hope that it may be possible to satisfy this requirement.

THE LIVER AND LACTATE METABOLISM—ROLE IN ACID–BASE REGULATION AND DISEASE

As indicated earlier in this review, the cycle of lactate production and consumption is normally in balance and so, therefore, are the inevitable concomitants of proton production and consumption. When production exceeds consumption, lactate acidosis results. By far the most common situation in which this occurs is in shock (Type A lactic acidosis). In recent years there has been much progress in the elucidation of the phenomenon of delivery-dependent oxygen consumption in patients with circulatory compromise, and the peripheral generation of lactate and proton which accompanies this stage of shock. However, the compromising of the lactate disposal mechanism during shock is also of major importance in the pathogenesis of Type A lactic acidosis. As the liver is responsible normally for up to 70% of lactate disposal [14], the determinants of hepatic uptake of lactate in both health and disease (blood concentration of lactate; hepatic blood flow; transit of lactate across the hepatocyte plasma membrane; metabolism—mainly gluconeogenesis; hormonal environment) are important subjects for study. Since in many respects they are interactive, they will be discussed together.

In the non-ischaemic rat liver, uptake of lactate (and generation of bicarbonate) increases progressively until the blood concentration of lactate reaches 4–5 mmol $litre^{-1}$ (normal 0.5–1 mmol $litre^{-1}$), and then reaches a plateau. There is some evidence in normal man that a similar plateau is reached at about 3 mmol $litre^{-1}$. In perfused rat liver, keeping the perfusate lactate constant at 2 mmol $litre^{-1}$, there is a slow decline in uptake of lactate with progressive ischaemia down to 25% of normal flow, and then a very much more rapid decline [25]. Mathematical modelling suggests that the initial slowness of the decline is the result of offsetting the decrease in delivery of lactate to the liver per unit time by the increased residence time of each unit volume of blood in the hepatic sinusoids, thus allowing more opportunity for uptake of the available lactate. Below 25% normal flow, there is a decrease in the intrinsic capacity of the liver cells to dispose of lactate; this coincides roughly with a decrease in liver cell ATP concentration and cell pH.

The first step in hepatic disposal of lactate is entry into the liver cell. This occurs by at least two mechanisms [10]: the first via a semi-specific monocarboxylate transporter [16, 17, 31] and the second by simple diffusion of the unionized moiety (lactic acid) [11]. The lactate transporter is activated by a pH gradient acid (outside) to more alkaline (inside), has a K_m for lactate (lactate concentration at which transport is 50% of maximal) of approximately 2 mmol $litre^{-1}$ [16, 17, 31], is largely stereospecific for the L-isomer, and is inhibited by a number of natural and pharmacological agents (D-hydroxybutyrate, cyano-cinnamate derivatives, phloretin). In rat hepatocytes, the activity of the transporter is markedly increased by starvation and diabetes, perhaps through an increase in transporter numbers per cell. Although it is controversial [16, 17, 31] if the lactate transporter is rate-limiting at physiological temperatures for uptake of lactate in isolated hepatocytes, there is evidence that it is so in intact perfused livers from starved rats [30]. The transporter increasingly saturates at lactate concentrations greater than 2 mmol $litre^{-1}$ and, in the environment of increased lactate concentration associated with shock, most of the lactate entry is likely to be through the diffusion pathway, which is first order and does not saturate. We suggested that, at decreased or normal blood concentrations of lactate, the diffusion permeability of the hepatocyte plasma membrane for lactate is insufficient to supply the increased requirement for lactate for gluconeogenesis in starvation and that the lactate transporter, with its appropriate K_m, is designed to overcome this problem.

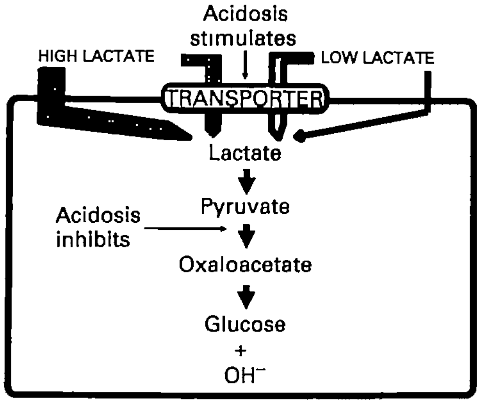

FIG. 2. Suggested model of the effects of acidosis on hepatic uptake and disposal of lactate. The enclosed area represents a liver cell. In the top right hand corner is depicted the situation with blood concentrations of lactate up to approximately 2.0 mmol litre^{-1}; a large element of lactate entry is via the transporter, which is stimulated by acidosis. The top left hand corner represents the situation with greater concentrations of lactate (3.0 mmol litre^{-1}), at which the transporter is saturated and the main pathway is diffusion. Intracellular acidosis inhibits the gluconeogenic pathway at the step indicated.

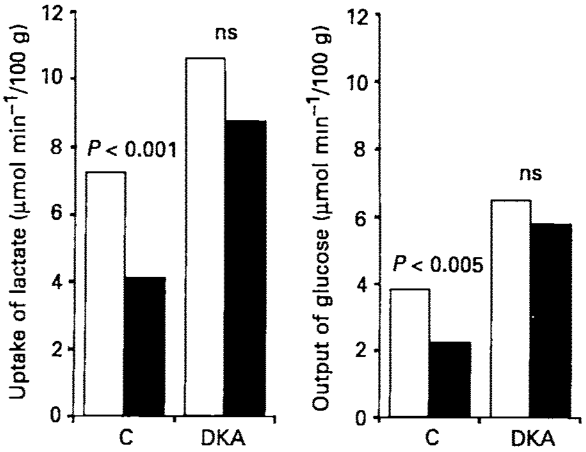

FIG. 3. Uptake of lactate and output of glucose in livers from control (C) and diabetic ketoacidotic (DKA) rats perfused with lactate 5 mmol litre^{-1} at either pH 7.4 (□) or pH 6.8 (■). For explanation see text. (Data from [7].)

After entry of lactate into the hepatocyte, the main pathway of disposal of lactate and concomitant regeneration of bicarbonate is gluconeogenesis. This pathway is inhibited by intracellular acidosis, whether of metabolic or respiratory origin [6, 27]; the site of this inhibition is at a stage between pyruvate and oxaloacetate, possibly at the pyruvate carboxylase level [25]. Putting these experimental observations together, we suggest (fig. 2) that any mild tendency to lactic acidosis (as a result of, for example mild exercise or minor blood loss) is counteracted by stimulation of the transporter, both by the mild increase in blood concentration of lactate and the decrease in extracellular pH relative to intracellular pH; the diffusion pathway is affected similarly. These effects increase removal of lactate and generation of bicarbonate and correct the acidosis, thereby providing another acid–base regulatory system intrinsic to the liver. However, during shock, the transporter mechanism is saturated and inhibition of gluconeogenesis at the pyruvate–oxaloacetate stage cannot be overcome by increased entry of lactate into the cell. It should be noted that the system is then unstable in an acute homeostatic sense, as the very failure of gluconeogenesis itself tends to decrease intracellular pH further because of failure of bicarbonate production. Normally, the greater the rate of conversion of lactate to glucose, the more alkaline the hepatocyte [12], although nearly all the bicarbonate produced is exported to compensate for peripheral bicarbonate titration (see above). Conversely, failure of gluconeogenesis from lactate would be expected to acidify the cell and set up a vicious circle of inhibition of lactate entry and removal, increased lactic acidosis and further cell acidification which may contribute to the poor prognosis of lactic acidosis in shock.

It is instructive to compare the situation in shock with the severe lactic acidosis of maximal exercise. In the latter situation most of the conditions operating in shock are also evident—decreased hepatic blood flow, increased blood concentration of lactate with saturation of the transporter, severe systemic acidosis; the effect on hepatic cell pH is unknown. The important point, however, is that on cessation of exercise, the increased circulating lactate is disposed of by skeletal muscle, now supplied with sufficient oxygen to be able to metabolize lactate aerobically; the systemic acidosis is corrected (which clearly is not possible in critically ill patients) and the vicious spiral is interrupted.

Most of the experimental work on perfused liver which attempted to simulate conditions seen in shock had been done in the absence of known endocrine influences on gluconeogenesis from lactate. Stress related hormones (glucagon, catecholamines, vasopressin and angiotensin) all stimulate gluconeogenesis from lactate by one or more of the following effects [34]: inhibition of

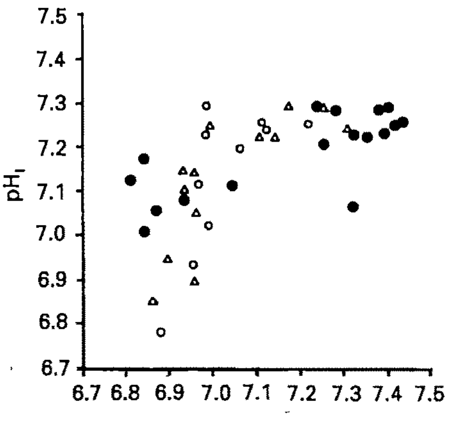

FIG. 4. Relationship of systemic pH (pH$_e$) to hepatic intracellular pH (pH$_i$), measured by phosphorus-31 magnetic resonance spectroscopy, in lightly anaesthetized rats made acidotic by ingestion of ammonium chloride (△), hydrochloric acid (○) or streptozotocin induced diabetes (●). Each point represents observations from a single animal. (From [7], reproduced by permission of the *Biochemical Journal*.)

pyruvate kinase by cyclic AMP-dependent phosphorylation, inhibition of production of fructose 2,6-biphosphate and stimulation of its removal, thereby inhibiting 6-phosphofructose 1-kinase and enhancing fructose 1,6-bisphosphatase. Steroids enhance transcription of the phosphoenolcarboxykinase gene, again providing for increased flux through the gluconeogenic pathway. It has been shown that addition of adrenaline (in concentrations simulating those seen in haemorrhagic shock in man) to blood perfusing the moderately ischaemic and acidotic rat liver can markedly improve the rate of disposal of lactate [14]. Observations in cultured rat hepatocytes suggest that glucocorticoids can increase the activity of the lactate transporter [29].

DIABETIC KETOACIDOSIS

Some of the most severe instances of metabolic acidosis occur in diabetic ketoacidosis (DKA). Lactic acidosis is a well described accompaniment of DKA, but it is relatively rare [13]. This point had always seemed to us a considerable difficulty in formulating the scheme of pathogenesis of lactic acidosis outlined above, for here was a very severe acidosis, in which the excessive protons concerned were produced presumably in the liver and should have caused a decrease in hepatic intracellular pH which would have both inhibited gluconeogenesis from lactate and prevented entry of lactate into the liver cell, both on the transporter and via the non-ionic diffusion route. We would, therefore, have expected lactic acidosis to be a regular rather than comparatively rare accompaniment of DKA. In contrast, it is known that *increased* gluconeogenesis from lactate and other substrates is the principal cause of hyperglycaemia in DKA. We aimed, therefore [7], to resolve this anomaly, either by demonstrating that the proposed scheme of pathogenesis of lactic acidosis simply was inconsistent with the experimental data, or by discovering some flaw in our reasoning of what should be the consequences of lactate metabolism in diabetic ketoacidosis.

Drs Beech and Iles in this laboratory attempted first to discover if gluconeogenesis from lactate was inhibited by simulated metabolic acidosis in perfused livers from rats with DKA, in the same way as is the case in livers taken from normal animals. The livers were perfused with lactate 5 mmol litre^{-1}—in excess of the K_m of the transporter, so that changes in transporter function would not distort interpretation of the results. The results are summarized in figure 3; it may be seen that whether "DKA" livers were perfused at normal or decreased pH, their rates of uptake of lactate and production of glucose were considerably greater than in normal livers. When the pH of the perfusate was decreased from 7.4 to 6.8 (by changing bicarbonate content, keeping $P\text{CO}_2$ constant), the normal livers exhibited a highly significant decrease in uptake of lactate and output of glucose, as demonstrated previously [7]. In contrast, in the livers from DKA animals, although there were slight decreases in lactate uptake and glucose output, these were not statistically significant. It appears, therefore, that the DKA livers are resistant to acidotic inhibition of gluconeogenesis from lactate and that this phenomenon persists despite isolation and perfusion in a hormone-free environment.

What was the reason for this apparent protection against acidotic inhibition? The first hypothesis to be tested was that, for some reason, hepatic intracellular pH did not behave as predicted in DKA. To examine this, rats were made acidotic by one of three methods—ingestion of ammonium chloride, infusion of hydrochloric acid or induction of DKA by injection of streptozotocin. In each group there was, by design, a substantial variation in the degree of systemic acidosis produced. Hepatic intracellular pH (pH$_i$) was then measured *in vivo* using phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) with surface coils placed over the liver, and the results plotted against pH measured on blood taken from a preplaced right atrial cannula. The relationship of pH_i to systemic pH (pH_e) was the same in both the ammonium chloride and the hydrochloric acid groups of animals: there was little effect on hepatic pH_i as pH_e decreased to 7.05, and then a steep decline in pH_i as pH_e decreased further (fig. 4) [7]. In contrast, in the DKA animals there was very little decrease in pH_i over the whole range of pH_e, even down to 6.7. These patterns were statistically significantly different. It appears, therefore, that hepatic pH_i is especially, and perhaps uniquely, protected in DKA. Further evidence of this phenomenon was seen in later experiments in which livers from DKA and normal rats were perfused at pH 6.8 whilst in a magnetic resonance spectrometer. Mean pH_i in the DKA livers was 7.24, compared with 7.12 in normal rats ($P = 0.005$).

We suggest that this protection of hepatic pH_i in DKA explains why gluconeogenesis from lactate is not inhibited in DKA. The following is a speculative attempt to explain the mechanism of protection of pH_i in DKA, and why gluconeogenesis from lactate is not only not inhibited, but enhanced. In the normal situation, lactate is produced at the periphery, together with H^+. As described earlier, local and blood HCO_3^- is titrated by the H^+, with a resulting decrease in $[HCO_3^-]$. The lactate ion enters the liver, mainly on the transporter at the normal blood concentrations of lactate prevailing. The principal fate of the lactate entering the hepatocyte is gluconeogenesis, producing glucose and HCO_3^- in the manner described earlier in this paper. It is essential that the bicarbonate is exported rapidly, for otherwise the liver cell would swiftly be alkalinized beyond viability. The exported HCO_3^- corrects the decrease in $[HCO_3^-]$ originally produced at the periphery during the generation of lactate and H^+.

We suggest further that, in contrast to the above, the situation during developing DKA is as follows. The increased oxidation of free fatty acids produces concentration of intramitochondrial acetyl CoA, together with large quantities of ketone bodies and their accompanying protons. The increased concentrations of acetyl CoA stimulate gluconeogenesis from lactate by allosteric activation of pyruvate carboxylase, a rate-limiting enzyme in this pathway; thus more lactate than normal is converted to glucose, with corresponding extra associated production of HCO_3^-. However, instead of being exported as in the normal situation, this bicarbonate is neutralized by the protons produced in association with ketone bodies. If ketone body production and conversion of lactate to glucose were equal in amount, the bicarbonate from the latter would precisely neutralize the H^+ from ketogenesis. In man, what evidence there is suggests that these processes are of the same order of magnitude if production of lactate by the gut is taken into account. The result is that hepatic pH_i does not change appreciably, as is in fact observed, and gluconeogenesis would therefore not be inhibited by intracellular acidosis. Since the liver cell is maintained relatively alkaline, but the extracellular compartment is very acid, the pH gradient across the plasma membrane is particularly favourable for stimulation of the lactate transporter, which thereby gives further impetus to lactate uptake and disposal. Data from isolated hepatocytes suggest that a change from pH_e 7.4, pH_i 7.25 (normal) to pH_e 6.7, pH_i 7.2 (DKA) might result in a doubling of flux through the transporter, which is relevant, since in the animals studied with ^{31}P-MRS described above, blood concentration of lactate was approximately 1 mmol litre^{-1}, that is, less than the apparent K_m of the transporter. Entry by the diffusion pathway will also be enhanced, to an unknown extent, by the pH gradient.

If, in DKA, HCO_3^- produced as a by-product of gluconeogenesis and H^+ produced in ketogenesis mutually consume each other, it is clear that the liver cannot be the source of the systemic acidosis of DKA, although it certainly is the source of the ketoanions. What, then, is the reason for the acidosis in DKA? Because of the mutual consumption of H^+ and HCO_3^- in DKA, the bicarbonate lost at the periphery by titration during production of lactate is simply not replaced as it is in the normal situation. Effectively, therefore, the systemic proton excess of DKA is derived from the periphery, not the liver. In other words, DKA might be regarded as a subtle form of lactic acidosis in which lactate and H^+ have been produced peripherally at normal or, more likely, increased rates; the lactate has been removed by the liver, leaving the excess H^+ (or HCO_3^- deficit, which is equivalent). This view, of course, applies in complete form only if uptake of lactate by the liver exactly matches ketone body production; if lactate uptake is less than ketogenesis, then this reinterpretation would only partially be true.

The protection of hepatic pH$_i$ in DKA could underlie disruption of normal hepatic acid–base homeostasis through the mechanism proposed by Häussinger (see above). As indicated earlier, in acidosis net hepatic uptake of glutamine is converted to net release of glutamine and synthesis of urea, with associated production of H^+, is reduced. However, in DKA as opposed to other forms of acidosis, hepatic uptake of glutamine is maintained or enhanced [40]. This may be because of the preservation of hepatic pH$_i$ in this form of acidosis. In any case, this would be an inappropriate response to the acidotic challenge of DKA if it resulted in increased synthesis of urea with accompanying production of protons. It may also explain why, often in DKA, the plasma concentration of bicarbonate decreases more than would be expected from the increase in circulating ketone body concentrations (the increase in anion gap does not match the decrease in bicarbonate concentration), although other mechanisms have been proposed for this phenomenon [1].

The behaviour of the liver in DKA therefore provides a remarkable and complex example of disturbed acid–base regulation. From an evolutionary standpoint, it is not possible to guard against all events. Evolution may select injury and haemorrhage as mishaps for which it is essential to have protection against the metabolic consequences; it seems unlikely that diabetic ketoacidosis would have similar evolutionary priority.

CONCLUSIONS

This review has described a number of recent reinterpretations of acid–base pathophysiology which could have therapeutic consequences in the future. Many of the arguments and controversies have been discussed in more detail in [9].

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INDICATIONS FOR USE OF BICARBONATE IN PATIENTS WITH METABOLIC ACIDOSIS

A. I. ARIEFF

Identifying the indications for use of bicarbonate in patients with metabolic acidosis has led to a major controversy in the fields of intensive therapy, medicine and anaesthesia, with numerous editorials expressing disparate opinions over the past 4 years [9, 33, 64, 94]. There have been substantial disagreements between various groups over the indications, or lack of them, for the use of bicarbonate. This article reviews the rationale for use of sodium bicarbonate in the management of patients with metabolic acidosis.

CLASSIFICATION OF METABOLIC ACIDOSIS

Metabolic acidosis can be broadly defined as a condition characterized by an arterial pH less than 7.35 and a bicarbonate concentration less than 21 mmol litre^{-1} in the absence of arterial hypercapnia. These biochemical findings imply addition to the extracellular fluid of an acid load, which may be either exogenous or endogenous. When the body is presented with an acid load, there is titration by various fixed buffers, both intracellular and extracellular. The intracellular buffers consist primarily of proteins and polypeptides, while extracellular buffers include haemoglobin, plasma proteins and creatinine. In general, because of the buffering capacity of the body, there will be no change in the plasma concentration of bicarbonate until all fixed buffers have been exhausted. Thus, when patients with metabolic acidosis demonstrate a measurable decrease in plasma concentration of bicarbonate, the indication is that all other available intra- and extracellular buffers have been exhausted.

There are several varieties of metabolic acidosis, and one method of classification is on the basis of the "anion gap" [65]. The anion gap (AG) is defined as the molar concentration of sodium ($[\mathrm{Na}^+]$) in blood minus those of chloride ($[\mathrm{Cl}]$) and bicarbonate ($[\mathrm{HCO_3}^-]$) [34, 68]:

$$\mathrm{AG} = [\mathrm{Na}^+] - ([\mathrm{Cl}^-] + [\mathrm{HCO_3}^-]) \qquad (1)$$

(normal range 9–14 mmol litre^{-1}). Thus metabolic acidosis may be classified according to whether the anion gap is normal, decreased or increased. Increased anion gap metabolic acidosis includes those disorders of acid–base metabolism in which there is acidosis because of the presence of increased quantities of organic acid(s). Such organic acids may be either endogenous (ketoacids, lactic acid) or exogenous (salicylate, paraldehyde). Those forms of metabolic acidosis with normal or decreased anion gap are primarily the renal tubular acidoses.

It has been proposed that metabolic acidosis with increased anion gap can be further classified into those clinical conditions in which tissue hypoxia is either present or absent [3] (table I). Tissue hypoxia is present theoretically in all forms of lactic acidosis in general, the acidosis of cardiac arrest in particular, and in a substantial number of patients who are critically ill, even if the blood concentration of lactate is not increased [13]. This is because depressed total body oxygen utilization will not result in increased lactate production until a critically low rate of oxygen use is reached. At this critical value, arterial lactate concentration may increase quite rapidly, often giving the impression that there is an acute

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Acid–base equilibrium· metabolic acidosis, bicarbonate, buffers. Hypoxia Complications: arrest

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TABLE I. *Metabolic acidosis with and without tissue hypoxia*

With hypoxia	Without hypoxia
Cardiac arrest	Uraemic acidosis
Lactic acidosis	Renal tubular acidosis
Pulmonary oedema	Diarrhoeal illness
Gram negative sepsis	Exogenous intoxications
	Salicylate
	Methanol

disturbance of tissue oxygenation whereas, in fact, there has been depressed use of oxygen for some time [5, 13, 31]. Tissue hypoxia is, generally, not present initially in most other forms of metabolic acidosis, in particular diabetic ketoacidosis, uraemic acidosis, most exogenous intoxicants (ethylene glycol, paraldehyde, methanol), renal tubular acidosis and the acidosis of diarrhoeal disease [33]. It is particularly important to distinguish those metabolic acidoses which are associated with tissue hypoxia, because it appears that therapy of such disorders, which often includes administration of sodium bicarbonate ($NaHCO_3$), frequently makes the acidosis worse [25, 39, 99]. However, administration of sodium bicarbonate to patients who have metabolic acidosis which is not associated with tissue hypoxia is often beneficial [33].

OXYGEN AND HYPOXIC METABOLIC ACIDOSIS

Hypoxia and source of hydrogen ions

In most instances where there is metabolic acidosis in the presence of tissue hypoxia, the predominant extracellular acid anion will be lactate. Lactic acid is formed primarily by anaerobic glycolysis because of a deficiency of available oxygen. It must be borne in mind that the extracellular abnormalities associated with metabolic acidosis have no necessary relationship to the intracellular changes. In particular, the effects of hypoxia on the heart are substantially different from those in other tissues [40, 78, 100]. Contrary to common perceptions, most of the intracellular H^+ ion in patients suffering cardiac arrest comes not from lactic acid but from "metabolic" carbon dioxide [78] and H^+ ion from the hydrolysis of ATP [48, 105] (table II). In hypoxic states, there is increased anaerobic metabolism, with increased generation of metabolic carbon dioxide and decreased generation of ATP. A major mechanism for removal of H^+ ion from myocardial cells is via the Na^+–H^+ antiporter, with transport of H^+ out of cells in exchange for Na^+ ion [42]. Sodium is then transported back out of cells via the Na^+–K^+ ATPase system. This system is energy dependent. In the presence of hypoxia, less ATP is available, leading to progressive intracellular acidosis as a result of accumulation of metabolic carbon dioxide and H^+ ion.

TABLE II. *Sources of hydrogen ion in hypoxic metabolic acidosis*

Tissue H^+ ion	Blood H^+ ion
Hydrolysis of ATP	Lactic acid
Metabolic carbon dioxide	Other
Lactic acid	Short chain fatty acids
	Renal failure

Hypoxia and the cardiovascular system

In the development of lactic acidosis associated with tissue hypoxia, the critical factors are the performance of the heart and lungs, and the subsequent delivery of oxygen to the tissues. Because of this, it is important to review the regulation of systemic and myocardial oxygen delivery and utilization. The critical role of the heart in the development of lactic acidosis is often not appreciated [3, 4]. Similarly, total body oxygen utilization may be substantially impaired without a measurable increase in arterial lactate concentration [13, 31]. Finally, measurements of arterial blood-gas tensions and lactate concentrations are often of no use in determining the acid–base and oxygenation status of either the "whole body" or the heart [1, 13, 58, 78, 100].

Metabolic acidosis: hypoxic and normoxic

If one attempts to predict the response to therapy in patients with metabolic acidosis, it appears that a more useful classification of metabolic acidosis would be based on whether the condition is or is not associated with tissue hypoxia (table I). In general, when there is metabolic acidosis in the presence of tissue hypoxia, available tissue oxygen is not adequate for the individual's metabolic needs. Treatment of the metabolic acidosis with sodium bicarbonate tends to limit further the available oxygen and thus lead to increased production of lactate, actually worsening the metabolic acidosis (table III). However, if the metabolic acidosis is not

TABLE III. *Treatment of metabolic acidosis with sodium bicarbonate*

With hypoxia	Without hypoxia
Increase in blood $P\text{co}_2$	No change in oxygen utilization
Decrease in blood pH	No change in lactate production
Decrease in tissue O_2 delivery	Increase in arterial pH
Decrease in coronary blood flow	

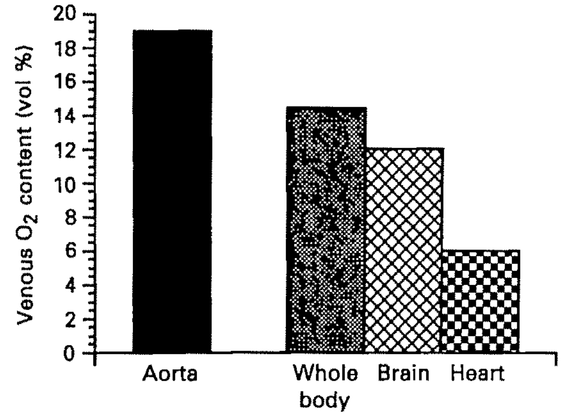

FIG. 1. Oxygen content in aorta and venous blood in normal humans. The oxygen extraction reserve may be calculated as the venous oxygen content as, in severe hypoxia, all available oxygen may theoretically, be extracted. It is apparent that the oxygen reserve of either "whole body" or brain is at least twice that of the heart. Thus in hypoxic states the heart has less oxygen reserve than any other organ or tissue in the body.

associated with tissue hypoxia (renal tubular acidosis, diarrhoeal illness, uraemic acidosis), bicarbonate may increase the arterial pH and prove beneficial [37, 76, 83] (table III).

In animals with hypoxic lactic acidosis, even with a mean arterial $P\text{o}_2$ as small as 4 kPa, the total body oxygen consumption appears not to change [5, 56]. This occurs largely because of the combined effects of increases in both cardiac output and oxygen extraction by the body. This combination has the effect that the actual amount of oxygen used does not change significantly (assuming the heart is capable of increasing its output). However, the distribution of oxygen use is not uniform. Oxygen utilization by gut, liver, kidney and muscle all decline. The result is an increase in production of lactate by gut and muscle, while extraction of lactate by liver decreases. Oxygen use by brain and heart almost certainly increases in the presence of tissue hypoxia. Thus hypoxic lactic acidosis is partly a result of a redistribution of available oxygen such that utilization by heart and brain are preserved, while that by gut, liver, kidney and skeletal muscle is not. These changes depend on the ability of the heart to increase cardiac output in response to a decreased arterial $P\text{o}_2$. If this response does not occur, the animal (or patient) will not survive. In patients with heart disease, the ability of the individual to increase cardiac output in response to a hypoxic situation is limited by the amount of reserve cardiac function, as well as the oxygen reserve described previously [12, 13, 18, 104] (fig. 1).

Another reason for the development of lactic acidosis relates to a decrease in hepatic lactate extraction. In hypoxia, this is probably related to both a decreased liver uptake of oxygen and a decrease in hepatic intracellular pH (pH_i) [73]. In summary, then, the pathogenesis of experimental hypoxic lactic acidosis is multifactorial. There is increased lactic acid production from both gut and skeletal muscle. The increase in production of lactate corresponds with a reduction of oxygen utilization by gut and skeletal muscle. Cardiac output, despite the presence of metabolic acidosis, is initially increased. Although it is commonly accepted that acidosis decreases cardiac output, in reality this is related to the pH_i of the heart, not the extracellular pH [39, 67, 95, 97]. In fact, survival of patients with cardiac dysfunction correlates best with myocardial ischaemia and intracellular acidosis [51]. The liver is unable to increase its lactate extraction to that which it ordinarily can achieve, and is associated with a highly significant decrease in hepatic pH_i, which is known to inhibit the ability of the liver to extract lactate. Lastly, impaired cardiac output, ischaemia (decreased organ blood flow) and extracellular metabolic acidosis do not appear to be important in the pathogenesis of hypoxic lactic acidosis.

BLOOD-GASES: ARTERIAL *VS* MIXED VENOUS

It is now clear from studies in both laboratory animals [6, 37, 58] and human subjects [1, 13, 100] that arterial blood-gas tensions are at best a poor indication of the acid–base and tissue oxygenation status of the body. Measurement of arterial blood-gas tensions evaluates the performance of the lungs, and the lungs can affect only the blood which has just passed through them. In low-flow states with impaired venous return, cardiac output, or both, arterial blood may be relatively normal while mixed venous blood demonstrates severe acidosis, hypoxia, or both [1, 100]. Measurements must be made of the arterial and mixed venous (pulmonary artery) gases, including oxygen content (which can be determined from the oxygen saturation and haemoglobin). As a practical matter, central venous gases are similar enough to mixed venous (pulmonary artery) gases that they can be used when a pulmonary artery catheter cannot be placed in the patient [1]. Oxygen transport (or delivery) may be calculated using the product of the arterial oxygen content and blood flow (usually expressed as oxygen ml min^{-1}). It represents the quantity of oxygen available or delivered to the whole body or to individual organs or tissues, and is maintained preferentially to the "vital organs" during hypoxia by a number of adaptive mechanisms [18, 43, 87]. The ability of tissues to increase oxygen extraction when oxygen delivery is inadequate is termed the oxygen extraction reserve or the oxygen utilization coefficient [20, 41, 88]. Because, in hypoxic states, tissues are theoretically capable of extracting virtually all of the oxygen carried to them by haemoglobin, the oxygen extraction reserve represents the amount of oxygen which is not extracted by tissues and, theoretically, is available [60]. Under normal aerobic conditions, this oxygen extraction reserve is quite large (fig. 1). However, because resting requirements for oxygen are greater per gram of tissue in the heart than in any other organ, resting oxygen extraction will be much greater there: about 60–65%. Consequently, the heart has the smallest extraction reserve, and can only increase resting oxygen extraction by a maximum of about 50%. This is in marked contrast to the body as a whole, which has an oxygen reserve which is three times the normal resting oxygen extraction (fig. 1). With profound hypoxia, circulatory adjustments become increasingly important to maintain adequate oxygen delivery to the heart and brain. There is a generalized reduction of oxygen utilization in most of the "non-vital" organs, such as skeletal muscle, liver and gastrointestinal tract, with preferential utilization by heart and brain. The failure of such adjustments leads to intracellular acidosis and eventual organ failure.

SODIUM BICARBONATE AND METABOLIC ACIDOSIS

General considerations

Sodium bicarbonate has been used in the treatment of metabolic acidosis for more than 50 years and has almost become a matter of routine. This practice was continued without any serious question of its metabolic and systemic actions until about 1980. The rationale has been the implied logic of administering a base to correct an acidotic state. Theoretically, sodium bicarbonate should react with the hydrogen ion from an organic acid:

$$HAc + NaHCO_3 \rightarrow NaAc + H_2O + CO_2 \quad (2)$$

where Ac represents the (an)ion of an organic acid.

The above reaction should remove the H^+ ion by its chemical conversion to water, with removal of the carbon dioxide via the lungs. In fact, in patients with renal tubular acidosis, diarrhoea and uraemic acidosis, the arterial pH frequently improves with the administration of sodium bicarbonate. Such patients generally do not have problems of tissue oxygenation, and in these situations bicarbonate often appears to be of benefit. However, administration of sodium bicarbonate has several disadvantages, including: venous hypercapnia with an increase in mixed venous carbon dioxide content [14, 44], leading to a decrease in tissue pH_i [6, 37, 86]; a decrease in the pH of cerebrospinal fluid [76, 79]; tissue hypoxia [12, 16, 55]; circulatory congestion [89]; hypernatraemia [59, 89]; hyperosmolality with brain damage [89, 90]. Whereas sodium bicarbonate is often of benefit in patients with metabolic acidosis in the absence of tissue hypoxia, some patients with diabetic ketoacidosis or hepatic failure will have impaired tissue oxygen delivery and the aforementioned complications of sodium bicarbonate are likely to develop. Additionally, in most patients with cardiac arrest, shock or sepsis, impaired tissue oxygen delivery is the primary cause of lactic acid accumulation. In these situations, the administration of sodium bicarbonate does not appear to affect the underlying tissue hypoxia and is generally not successful in improving either acidotic state or clinical status. Thus the underlying cause of lactic acid accumulation appears to dictate if the administration of sodium bicarbonate will be of benefit (table III).

In an early study of patients with lactic acidosis [99] given large amounts of i.v. bicarbonate, there was essentially no change in either arterial pH or the clinical condition of these patients. None survived. In patients with cardiac arrest, sodium bicarbonate increases the mixed venous and arterial $P\text{CO}_2$ [14, 59, 100] without either decreasing the blood concentration of lactate or increasing that of bicarbonate. The result is either no change or a net reduction of the blood pH when compared with observations if sodium bicarbonate is not used. Moreover, the administration of large amounts of bicarbonate (mean 180 mmol litre^{-1}) during cardiac arrest [59] resulted in severe hypernatraemia, hyperosmolality, increasing lactic acidosis and no survival. These observations and others have apparently led to continuing recommendations by the American Heart Association that the amount of bicarbonate administered to patients suffering cardiac arrest should be reduced. Current guides for the management of cardiopulmonary arrest no longer recommend the routine use of sodium bicarbonate [66].

Hypercapnia

The arterial $P\text{CO}_2$ is determined by the ratio of production of carbon dioxide to alveolar ventilation; it is directly proportional to production of carbon dioxide and inversely proportional to alveolar ventilation [101]. Thus increased generation of carbon dioxide by administration of bicarbonate will actually increase the venous $P\text{CO}_2$ if there is impaired cardiac output (because of decreased delivery of venous carbon dioxide to the lungs) or a decrease in alveolar ventilation. Carbon dioxide readily diffuses into cells such that the intracellular $P\text{CO}_2$ approaches that of mixed venous blood. In a closed system, carbon dioxide accumulates after administration of bicarbonate, thereby decreasing the pH [71]. The effects of decreased alveolar ventilation may be imitated by addition of sodium bicarbonate to a closed system *in vitro*. In an *in vitro* system, sodium bicarbonate did not normalize the pH of acidified blood [52]. These results and others utilizing sodium bicarbonate in an acidotic *in vitro* system demonstrate that it does not increase the pH of blood when there are constraints to the removal of carbon dioxide from the system [71]. Such a situation may occur clinically in states characterized by low pulmonary blood flow, such as heart failure, shock, cardiac arrest and haemorrhage. Numerous *in vivo* studies demonstrate that administration of i.v. bicarbonate to humans with either metabolic acidosis or heart failure results in an increase in blood $P\text{CO}_2$ [12, 25, 26, 57, 59, 78, 100, 102]. In laboratory animals with various forms of metabolic acidosis, i.v. administration of bicarbonate results in a decrease of pH_i in brain, liver, skeletal muscle and red blood cells [6, 36, 37, 39, 44, 86, 103].

Diabetic ketoacidosis

Indications for the use of bicarbonate in diabetic ketoacidosis are currently less controversial than had previously been the case. There are reports of at least two studies in which the effects of bicarbonate on blood pH, glucose, bicarbonate and ketone concentrations were examined in patients with diabetic ketoacidosis [53, 63]. In general, it was found that administration of bicarbonate did not result in either a greater decrease in blood concentrations of ketone or a more rapid increase in blood pH than was observed in patients who did not receive bicarbonate. Thus sodium bicarbonate administered to patients with diabetic ketoacidosis had no apparent effect on the rate of change in pH, blood ketone concentrations, the change in blood concentration of bicarbonate or arterial $P\text{CO}_2$. In addition, the ultimate survival rate was similar in patients who did or did not receive bicarbonate. Administration of sodium bicarbonate has been associated with an increase in spinal fluid $P\text{CO}_2$ which was not observed when bicarbonate was not given [8, 69]. This resulted in a small but significant decrease in the pH of cerebrospinal fluid. Earlier studies had suggested that such a decrease in spinal fluid pH secondary to administration of bicarbonate might lead to depression of the sensorium [79]. However, subsequent studies have failed to confirm these earlier impressions [76]. Although the reduction in spinal fluid pH may not be harmful, it is almost certainly of no benefit. Evidence that bicarbonate may be harmful to patients with ketoacidosis is found in other studies. In animals with metabolic acidosis, administration of bicarbonate decreased delivery of oxygen to the brain, increased cerebrospinal fluid concentrations of lactate and decreased brain intracellular pH [16, 86].

Another reason why the use of bicarbonate in patients with diabetic ketoacidosis may not be useful relates to the stoichiometry of the disorder. In ketoacidosis, there is at least 400–500 mmol of available endogenous bicarbonate precursor in the

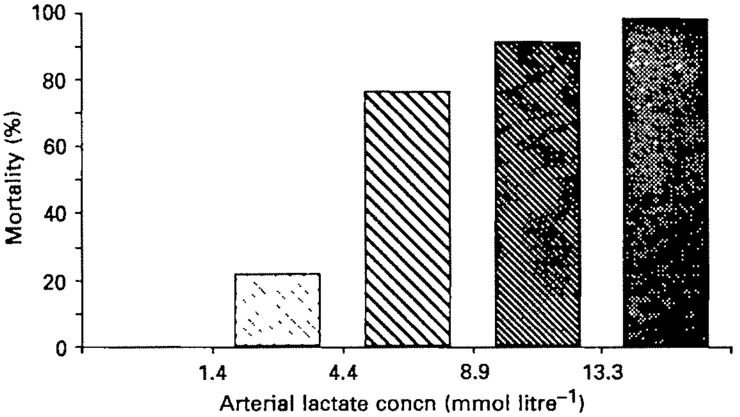

FIG. 2. Mortality of lactic acidosis as a function of the initial arterial concentration of lactate. There is an increasing mortality with increasing lactate concentration such that a value greater than 9 mmol litre^{-1} carries a mortality in excess of 90% [23, 75].

form of lactate and ketoacid anions. The liver is able to metabolize these anions, and for each 1 mmol metabolized, 1 mmol of H^+ ion is consumed and a bicarbonate ion is generated [10, 21]. Thus, in patients with diabetic ketoacidosis, the body has more than 400 mmol of available bicarbonate precursor, and with insulin administration, ketogenesis (a H^+ ion generating reaction) ceases. Administration of the 50–100 mmol of bicarbonate given commonly to patients with diabetic ketoacidosis would therefore not be expected to influence arterial pH and, in practice, it generally does not [63]. Overall, it appears that there are few if any beneficial effects attributed to the use of bicarbonate in patients with ketoacidosis, and there are several potentially harmful mechanisms. The clinical importance of these mechanisms remains to be established.

Lactic acidosis

Lactic acidoses is probably the most common form of metabolic acidosis and is generally defined as metabolic acidosis resulting from the accumulation of lactic acid, with blood lactate concentration in excess of 5 mmol litre^{-1} and blood pH less than 7.25. The mechanisms by which lactic accumulation occurs vary, and include both the stimulation of production of lactate and reduction in lactate metabolism. Clinically, disorders of lactate metabolism have traditionally been classified as either anaerobic (Type A) or aerobic (Type B) [22, 23]. The hallmark of Type A lactic acidosis is tissue hypoxia resulting in anaerobic lactic acid production. Such disorders include cardiopulmonary arrest and other states (such as shock, haemorrhage, pulmonary oedema) characterized by impaired cardiac performance, reduced tissue perfusion and arterial hypoxaemia. Type B lactic acidosis is not associated with tissue hypoxia, but there is increased production of lactic acid, for other metabolic reasons. Examples of Type B lactic acidosis include diabetes mellitus, certain malignancies and congenital disease of the liver which impair lactate metabolism. Of the two forms of lactic acidosis, Type A is more common clinically and generally is associated with a greater morbidity and mortality.

Hyperlactataemia is far more than an isolated laboratory finding. It has been observed consistently that when the blood concentration of lactate exceeds 9 mmol litre^{-1}, mortality exceeds 75% (fig. 2) [75]. This formulation excludes those clinical conditions in which lactate is acutely and reversibly increased, such as following grand mal seizures or strenuous anaerobic exercise [70].

Lactic acidosis and the cardiovascular system

Lactic acidosis appears to have negative effects on myocardial function which are both direct and indirect, and are present when the acidosis is caused by either hypercapnia with hypoxia or metabolic acidosis *per se* [47, 67, 97]. However, recent data strongly suggest that, after myocardial ischaemia (as a result of cardiac arrest or coronary occlusion), myocardial pH_i may decrease to less than 6.0 [51], not as a result of H^+ ions derived from myocardial lactate accumulation, but rather as a result of a combination of H^+ ion from the

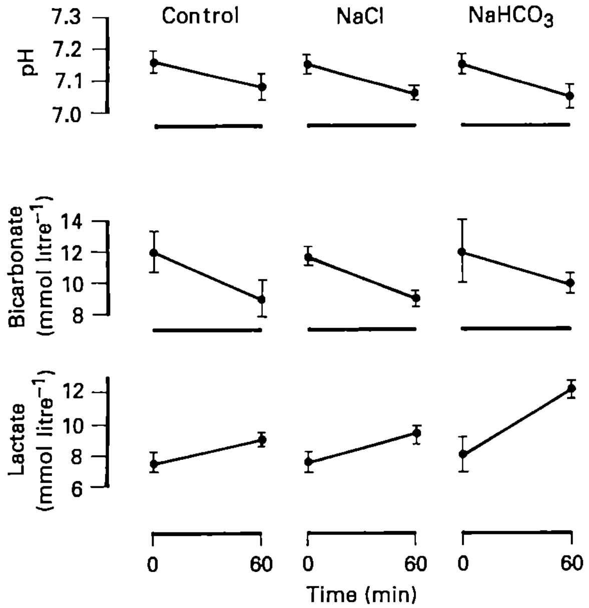

FIG. 3. Effects of i.v. bicarbonate ($NaHCO_3$) compared with saline (NaCl) or no therapy (control) in dogs with hypoxic lactic acidosis (arterial P_{O_2} less than 4 kPa). After administration of $NaHCO_3$, there is a continuous decline in both arterial blood pH and bicarbonate concentration, with an increase in lactate concentration. With equimolar NaCl, the changes in arterial blood pH and bicarbonate concentration are similar. (Figure from [39], by permission of *Science*.)

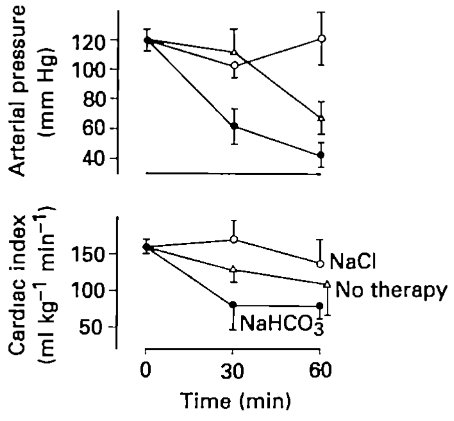

FIG. 4. Effects of i.v sodium bicarbonate (●) compared with NaCl (○) or no therapy (△) in dogs with hypoxic lactic acidosis (arterial P_{O_2} less than 4 kPa). After administration of $NaHCO_3$, there is a steady decline in both arterial pressure and cardiac output, while with equimolar NaCl, there is no change. (Figure from [39], by permission of *Science*.)

hydrolysis of ATP [48, 105] and "metabolic" hypercapnia [50, 78, 97]. Furthermore, the acid–base status of the heart and coronary circulation is not accurately reflected by the arterial blood chemistry [1, 78]. Since effects on the myocardium are largely determined by myocardial pH_i and not the extracellular pH, it is not appropriate to administer sodium bicarbonate on the basis of arterial gases [100]. Nonetheless, the development of myocardial intracellular acidosis is known to be associated with depression of myocardial mechanical function [2, 61]. The goal of cardiopulmonary resuscitation has been to correct rapidly both hypoxia and metabolic acidosis, in order to promote the recovery of myocardial function. However, sodium bicarbonate has not been shown consistently to improve haemodynamics, increase arterial pH or increase the blood concentration of bicarbonate, and it appears to have adverse effects on both tissue oxygenation and myocardial function [26, 36, 39, 57, 91, 93].

Animal experiments have demonstrated that, in hypoxic metabolic acidosis, sodium bicarbonate neither increases arterial pH nor affects plasma bicarbonate concentration (fig. 3) [39]. As a consequence, administration of sodium bicarbonate to animals with hypoxic metabolic acidosis causes a decline in both systemic arterial pressure and cardiac output (fig. 4). Additionally, studies in several different animal models have confirmed that the administration of sodium bicarbonate in hypoxic states causes a reduction in tissue pH_i in liver, skeletal muscle, red cells and brain [6, 16, 37, 44, 103]. The mechanism of the reduction in pH_i has not been elucidated completely, but probably involves increased breakdown and decreased synthesis of ATP [48], increase in intracellular tissue concentration of lactic acid and increased tissue production of carbon dioxide [35, 40, 78]. Clinically, the mixed venous P_{CO_2} increases disproportionately in cardiac arrest [19, 100], causing severe venous acidosis which may not be reflected by arterial blood-gas analyses [1, 35]. In this setting, the administration of sodium bicarbonate may aggravate intracellular and extracellular acidosis by accelerating production of carbon dioxide [35, 40, 50, 77].

ALTERNATIVES TO SODIUM BICARBONATE

Possible detrimental effects of bicarbonate may be summarized as: venous hypercapnia, decrease in intracellular pH, cerebrospinal fluid acidosis, tissue hypoxia, circulatory congestion and hypernatraemia. Because of these varied effects on organ function (particularly that of the heart) during hypoxic states, several other agents have been developed for the treatment of Type A lactic acidosis. The goal has been to improve the blood pH during hypoxic states without reducing oxygen delivery, stimulating production of carbon dioxide or lactate, or adversely affecting end organ function. The most promising of these agents are Tris buffer (2-amino-2-hydroxymethyl-1,3-propanediol) (THAM), Carbicarb and dichloroacetate. All have been tested in human subjects with metabolic acidosis but, as of March 1991, none has been approved for use in humans [11, 15, 24, 30, 93, 103].

Dichloroacetate

Sodium dichloroacetate (DCA) may be an effective and safe form of therapy for reducing lactate concentrations and increasing pH in lactic acidosis. The effects of this drug on intermediary metabolism have been studied extensively in normal animals and in several animal models of lactic acidosis [28, 74, 92]. In animals with increased lactate concentrations induced by exercise, diabetes, endotoxin, sepsis, phenformin, hepatic insufficiency, adrenaline or hypoxia, administration of DCA results in a reduction in the concentration. In dogs with lactic acidosis caused by hypoxia, diabetes or phenformin, i.v. administration of DCA improved both intracellular and systemic pH [38, 72].

To date, the effects of DCA in the treatment of lactic acidosis have been described in several clinical studies involving both adults and children [15, 27, 45, 46, 92–94]. More than 80% of the patients in these studies responded to treatment, defined by at least a 20% reduction in blood concentration of lactate occurring within 6 h of the first dose of DCA. Administration of DCA did not change the arterial or mixed venous $P\text{CO}_2$ values, and thus presumably does not result in intracellular accumulation of carbon dioxide [74, 93]. There have been no reported adverse effects of oral or parenteral administration of DCA in children or adults with lactic acidosis. Based on these preliminary data, a multi-centred, controlled clinical trial is currently in progress to evaluate the effect of DCA therapy on morbidity and mortality in adult patients with acquired causes of lactic acidosis [29]. Initial results from this study should become available within the next year.

In animal studies, dichloroacetate increases arterial pressure, cardiac output, oxygen delivery, liver pH_i and liver uptake of lactate in dogs with either phenformin-induced [72, 74] or hypoxic [38] lactic acidosis (fig. 5). It is not known if DCA affects tissue oxygen extraction *in vivo* or if DCA alters myocardial pH_i; however, there is substantial improvement in myocardial performance following administration of DCA. Such effects include increased cardiac output and stroke work, myocardial efficiency index, and increased intramyocardial concentrations of ATP and improvement in the ECG [17, 62, 80, 98]. Clearly, the mechanisms by which DCA improves cardiovascular function in hypoxic lactic acidosis are complex. However, both in patients with lactic acidosis and in animal models with hypoxic lactic acidosis, administration of DCA improves cardiac output, while bicarbonate decreases both arterial pressure and cardiac output [38, 39, 72, 93]. It is clear that, in patients with lactic acidosis, DCA improves arterial blood-gas tensions and decreases blood lactate concentrations. Improved survival has not yet been demonstrated.

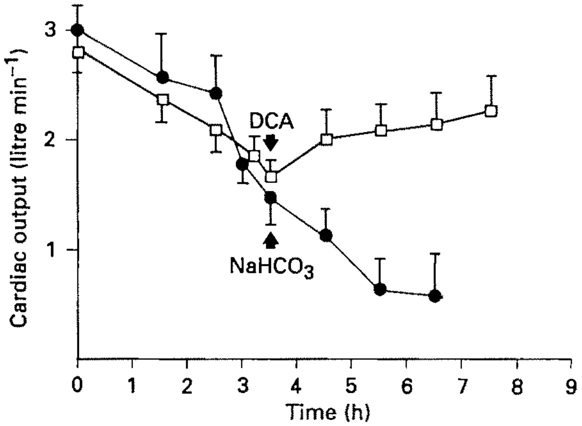

FIG. 5. Effects of i.v. sodium bicarbonate (NaHCO_3) (●) compared with that of dichloroacetate (DCA) (□) in dogs with phenformin-induced lactic acidosis [7]. With DCA, there is restoration of cardiac output to normal, while with bicarbonate the cardiac output declines to values incompatible with life. (Figure from [72], by permission of the *Journal of Clinical Investigation*.)

Carbicarb

Carbicarb was described in 1984 [32] as a potential replacement for sodium bicarbonate in the therapy of metabolic acidosis [52]. It is an equimolar solution of sodium bicarbonate and sodium carbonate [11]. It buffers acids in a similar manner to the action by sodium bicarbonate but without increasing the blood concentration of carbon dioxide. This permits an evaluation of the hypothesis that generation of carbon dioxide after administration of sodium bicarbonate causes many of the detrimental effects on lactate metabolism and cardiovascular function [52]. Studies using sodium bicarbonate in an acidotic *in vitro* system demonstrate that bicarbonate will not increase the pH of blood when there are constraints to the removal of carbon dioxide from the system [71], such as in circulatory congestion or shock. In normal volunteers, administration of sodium bicarbonate resulted in a marked increase in excretion of carbon dioxide, whereas administration of Carbicarb resulted in a decrease in $P\text{CO}_2$ [85]. These results suggested that Carbicarb actually decreased generation of carbon dioxide when administered systemically.

Carbicarb was compared with sodium bicarbonate in rats with metabolic acidosis induced by asphyxia [96]. In rats with an arterial pH of 7.17, sodium bicarbonate did not increase arterial pH, but resulted in significant increases in both $P\text{CO}_2$ and lactate concentration. With Carbicarb, there was a significant increase in arterial pH, but no change in lactate concentration or $P\text{CO}_2$. In another study, rats were made acidotic by either ammonium chloride or respiratory hypercapnia [86]. In the rats with ammonium chloride-induced acidosis, administration of sodium bicarbonate resulted in a decrement of brain pH_i with an increase of arterial $P\text{CO}_2$. Carbicarb normalized arterial pH without an increase in arterial $P\text{CO}_2$, and the pH_i of brain was alkalinized [86]. In the rats with respiratory hypercapnia, sodium bicarbonate intensified the hypercapnia. In a model of cerebral ischaemia, administration of sodium bicarbonate resulted in an increase in brain $P\text{CO}_2$ with a decline in brain pH_i [44].

In a laboratory study [11], 28 dogs with hypoxic lactic acidosis were treated with 2.5 mmol litre^{-1} kg^{-1} of either sodium bicarbonate or Carbicarb over 1 h. Measurements made after 1 h of hypoxia and then after 1 h of therapy comprised: cardiac haemodynamics, blood-gas tensions, liver pH_i, oxygen consumption and regional production of lactate. After treatment with Carbicarb, the arterial pH increased (from 7.22 to 7.27), but decreased after sodium bicarbonate (from 7.18 to 7.13). Mixed venous $P\text{CO}_2$ did not change with Carbicarb, but increased with sodium bicarbonate. Arterial lactate concentration stabilized with Carbicarb but increased with sodium bicarbonate. Use of lactate by muscle, gut and liver all improved with Carbicarb and decreased with sodium bicarbonate. Liver pH_i (normal = 6.99, hypoxia = 6.80) improved with Carbicarb (to 6.98), but decreased further with sodium bicarbonate (to 6.40). Muscle consumption of oxygen increased with Carbicarb, whereas it decreased with sodium bicarbonate. Arterial pressure decreased less and the cardiac output remained stable with Carbicarb, but decreased by 31% with sodium bicarbonate. Stroke volume also improved with Carbicarb without a change in pulmonary capillary wedge pressure, suggesting a beneficial effect on cardiac function. Thus administration of Carbicarb to dogs with hypoxic lactic acidosis results in improvement in the arterial blood-gas tensions, tissue pH_i, production of lactate and cardiac haemodynamics. The response to Carbicarb contrasts with the effects of sodium bicarbonate and may be related to reduced systemic generation of carbon dioxide by Carbicarb. Thus, in laboratory animals, Carbicarb appears to be superior to sodium bicarbonate for the treatment of hypoxic states with lactic acidosis. Clinical trials commenced in 1990.

THAM

THAM is a synthetic buffer which has been proposed for the treatment of metabolic and respiratory acidosis. Theoretically, it counteracts the effects of accumulation of carbon dioxide in respiratory acidosis [24] and has been shown also to be effective in the treatment of some forms of metabolic acidosis [54]. At physiological pH (7.38), THAM has a buffer capacity about the same as that of normal blood [54]. Unlike other buffers, such as bicarbonate, THAM penetrates cells and is an effective intracellular buffer. In dogs with metabolic acidosis, administration of sodium bicarbonate resulted in an increased extracellular pH (from 7.30 to 7.58), but no change in pH_i. However, with THAM, extracellular pH increased from 7.34 to 7.47, pH_i increased from 7.08 to 7.27, with an increase in intracellular bicarbonate from 11.6 to 21.4 mmol litre^{-1}. Thus, THAM readily penetrates certain cells and appears to be an effective intracellular buffer [82].

Studies have been carried out in isolated left ventricle preparations. Addition of THAM to the perfused left ventricle at physiological pH increased myocardial contractility during ischaemia [30]. However, without ischaemia, the inotropic effect was of smaller magnitude. Thus, in *in vitro* studies, THAM exerts an inotropic effect on ischaemic myocardium [30]. In an animal model of cardiac arrest, THAM did not improve survival when compared with bicarbonate [77]; however, this may be attributable to the fact that, overall, the particular animal model in question is not readily amenable to resuscitation, whatever the therapeutic intervention [35, 49, 77].

In preliminary clinical studies, THAM was used in the treatment of six patients with severe diabetic ketoacidosis (mean arterial pH = 7.12, bicarbonate = 8.8 mmol litre^{-1}). In all cases, THAM corrected the metabolic acidosis within 4–12 h without obvious toxicity [79]. In additional preliminary studies in five patients with acidosis of renal failure, THAM was successful in increasing the arterial pH in all five patients, again without obvious toxicity [82]. Thus, based on the effects of THAM on ischaemic myocardium *in vitro* [30], and *in vivo* effects on metabolic acidosis of several different etiologies [81, 82], THAM may be a valuable agent for the overall management of patients with lactic acidosis or cardiac arrest. Studies have not yet been carried out in either human subjects or animal models of lactic acidosis or cardiac arrest.

THAM, DCA and Carbicarb appear to be promising agents for the management of metabolic acidosis. All have been used in human subjects without apparent toxicity. At this juncture, none is approved for human use. Based on data in both laboratory animals and patients with various forms of metabolic acidosis, all appear to be superior to sodium bicarbonate in the management of metabolic acidosis, and it is hoped that these agents will be available for human use in the near future.

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CALCIUM FOR RESUSCITATION?

E. ERDMANN AND E. REUSCHEL-JANETSCHEK

Calcium ions are essential in myocardial excitation–contraction coupling, in augmenting myocardial contractility and in enhancing ventricular automaticity during asystole. Nevertheless, the use of calcium in cardiopulmonary resuscitation has recently come into dispute for several reasons [18, 23, 24, 31]: calcium may have deleterious effects, especially in ischaemic areas of the brain and the heart; inhibition of intracellular accumulation of calcium may be more beneficial than increasing calcium concentrations; and evidence for the successful use of calcium in cardiac arrest is rather scarce.

In this report we discuss some of the relevant data with respect to the efficacy of calcium in resuscitation, and describe our own experience with calcium infusions in end-stage severe heart failure (cardiogenic and septic shock).

EFFECTS OF CALCIUM ON THE MYOCARDIUM

There is no myocardial contraction unless a certain amount of extracellular calcium is present. Figure 1 shows the concentration–response curve for calcium in electrically stimulated isolated human papillary muscles *in vitro*. It shows clearly that the isometric force of contraction increases as the extracellular concentration of calcium is increased.

The mode of action of calcium in the cardiac muscle cell can be summarized as follows:

(a) The extracellular concentration of calcium is approximately 2.5 mmol litre^{-1}, whereas the intracellular concentration is about 0.1 µmol litre^{-1}. After excitation, calcium enters the myocardial cell mainly during the plateau phase of the action potential through the "slow calcium channel" in the cell membrane (fig. 2).

(b) The cardiac cell contains much greater concentrations of calcium than are necessary for initiating contraction. Most of this intracellular calcium is, however, bound within the sarcoplasmic reticulum (SR) and therefore is not permanently available. When the cell is depolarized and some small amounts of Ca^{2+} cross the cell membrane, they trigger the release of large quantities of Ca^{2+} from the SR into the cytoplasm, activating the contractile proteins.

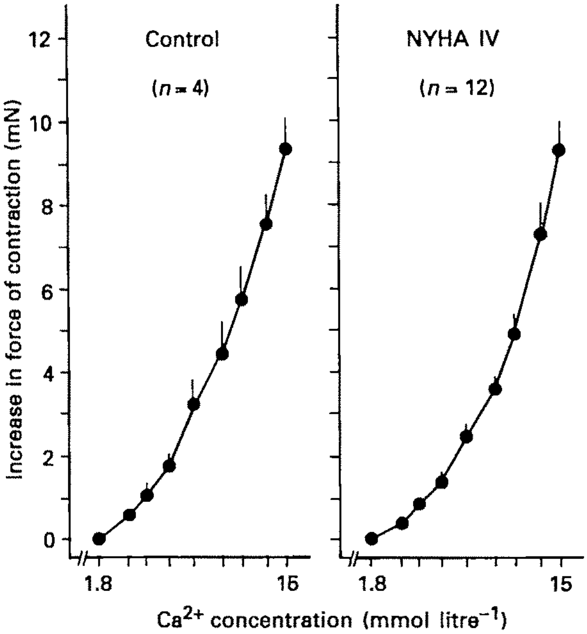

FIG. 1. Effect of calcium on force of contraction in the human left ventricular papillary muscle. Muscles were obtained from patients undergoing heart transplantation (end-stage heart failure, NYHA IV) or from hearts which could not be used for transplantation because of technical difficulties. Muscle strips were stimulated electrically (1 s^{-1}) in a modified tyrode solution. Isometric force of contraction was recorded. It can be seen that the concentration–response curves for Ca^{2+} are not different in healthy (control) and severely failing (NYHA IV) human heart. (For experimental details see [3].)

KEY WORDS
Ions: calcium. Heart: resuscitation.

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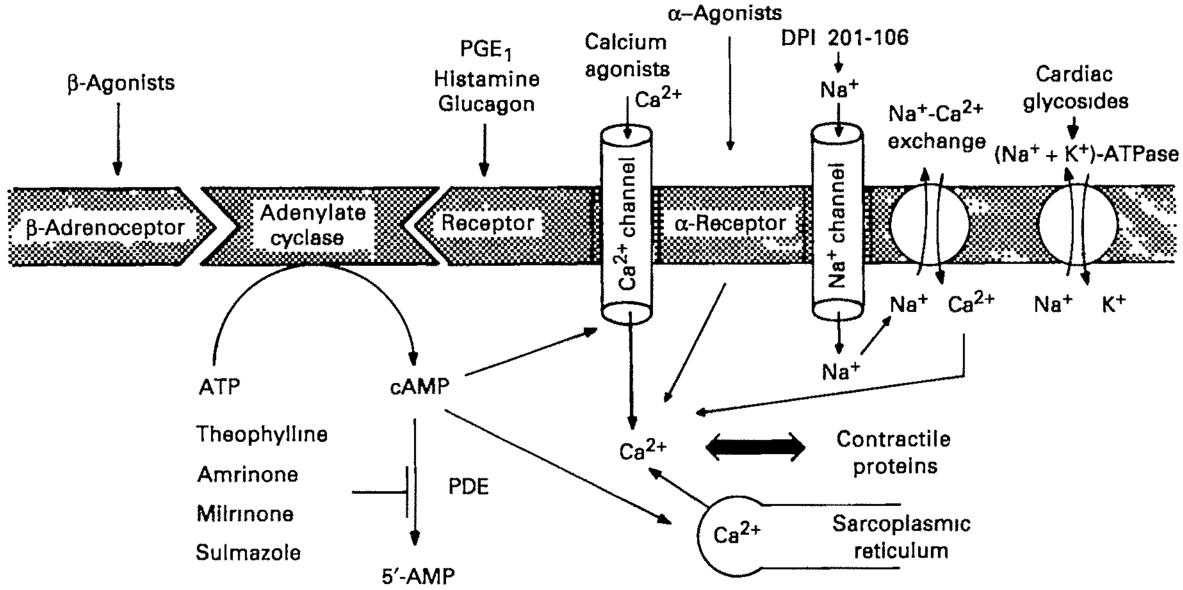

FIG. 2. Simple scheme of the central role of calcium in cardiac contraction. Mitochondria take up calcium only if cytoplasmic concentrations of calcium are extremely large.

(c) Relaxation occurs when calcium is taken up again actively by the SR, but other mechanisms are needed also to extrude calcium from the cell: the Na^+–Ca^{2+} exchange system of the cell membrane, a calcium ATPase in the sarcolemma and other enzymes within the SR. It appears that mitochondria take up calcium only when cytoplasmic concentrations of calcium are extremely great. If accumulated within mitochondria, calcium impairs the generation of ATP and thus contributes to cell death (calcium overload).

(d) Several factors influence cellular calcium homeostasis: extracellular calcium concentration, circulating catecholamines, rate of stimulation, cardiac glycosides, etc. It is noteworthy that a reduction in intracellular pH results in a decreased release of Ca^{2+} from the SR and thus in impaired myocardial contraction.

(e) In severe ischaemia the cell loses its ability to maintain calcium homeostasis. Calcium enters the cell passively through the damaged cell membrane and through its usual pathways. The small concentrations of intracellular ATP during ischaemia are not sufficient to extrude this increased amount of intracellular Ca^{2+}, which then activates proteases and phospholipases that further contribute to cell and cell membrane damage. Following reperfusion, the cytoplasmic excess Ca^{2+} is partly taken up by the mitochondria in a process that consumes energy (ATP). Because of this calcium accumulation, the mitochondria become unable to produce ATP. Continued intracellular accumulation of calcium may initiate arrhythmias, myofibrillar contracture and, eventually, cell death (fig. 3).

(f) In animal experiments, verapamil seems to have a protective effect on ventricular fibrillation occurring after coronary artery occlusion. This beneficial role of calcium antagonists in preventing ischaemic ventricular fibrillation operates by preventing the accumulation of intracellular calcium, and is reversed by addition of calcium chloride.

STUDY OF CALCIUM IN CARDIOGENIC AND SEPTIC SHOCK

We have studied 28 patients (age 18–67 yr (mean 55 yr); 10 female, 18 male) with terminal heart failure (cardiogenic shock or the hyperdynamic form of septic shock) who were monitored by right heart catheterization in the critical care unit. Twenty had a history of dilated cardiomyopathy and eight, one of ischaemic cardiomyopathy; they were included in the study because systolic arterial pressure was $\leqslant$ 90 mm Hg in spite of concomitant therapy comprising dopamine 5–20 $\mu g\ min^{-1}\ kg^{-1}$ and dobutamine 30 $\mu g\ min^{-1}\ kg^{-1}$. In most, nor-

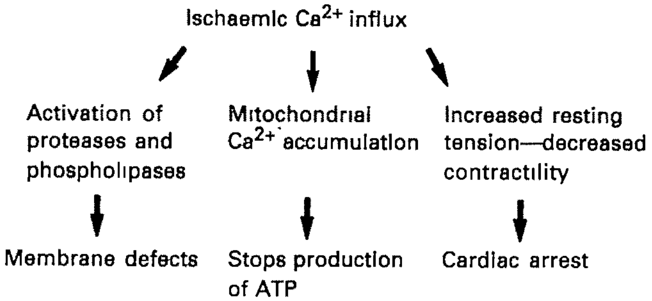
Ischaemic Ca^{2+} influx
Activation of proteases and phospholipases
Mitochondrial Ca^{2+} accumulation
Increased resting tension—decreased contractility
Membrane defects
Stops production of ATP
Cardiac arrest

FIG. 3. Effects of severe ischaemia on calcium homeostasis.

adrenaline up to 25 μg kg^{-1} min^{-1} and adrenaline up to 15 μg kg^{-1} min^{-1} was necessary to maintain this pressure. In one patient with a severe form of hypodynamic septic shock, angiotensin also was given (25 ng kg^{-1} min^{-1}).

Two patients with most severe cardiogenic shock were treated by intra-arterial balloon pulsation; six of the patients were treated also with digitalis. In all patients at least three haemodynamic measurements by right heart catheterization had been performed within 12 h preceding the study period, and all treatment was stabilized. All patients were anuric and treated by arteriovenous haemofiltration.

After a steady state of 12 h (with constant haemodynamic variables and constant therapy), 20% calcium gluconate 10 ml (containing Ca^{2+} 4.5 mmol) (Calcium-Sandoz) was given by continuous i.v. infusion at 20 mmol h^{-1} over 30 min. This infusion of calcium had proved to be efficacious in previous investigations and was therefore applied to all patients. Haemodynamic measurements were performed just before each infusion period and after each 30-min infusion. In all patients fluid balance was maintained by regulation of the arteriovenous haemofiltration.

Haemodynamic monitoring was performed by continuous measurement of arterial pressure using a radial or femoral artery catheter and right heart catheterization by a triple-lumen, balloon-tipped thermodilution pulmonary artery catheter (Swan–Ganz). Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), right atrial pressure (RAP), mean pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP) were measured after calibration (zeroing to atmospheric pressure, referenced to the mid-chest level) using strain-gauge transducers (Gould Statham P50). PCWP was measured at end-expiration (none of the patients was ventilated using positive end-expiratory pressure). Cardiac output (CO) was measured in triplicate, after injection of 10 ml of ice-cold saline, using a cardiac output computer (Sirecust 404-1, Siemens). Systemic vascular resistance (SVR) was calculated according to the formula: $SVR = (MAP - RAP).80/CO$ (dyn s cm^{-5}).

Data were summarized by mean, SD and range. For comparison between the groups, the paired *t* test was applied.

Serum concentrations of calcium increased in most patients. Large increases in mean SAP and SVR were observed, whereas CO and stroke volume increased only slightly (fig. 4). Heart rate, RAP and PCWP did not change significantly. The observed haemodynamic effects (fig. 4) seemed to be more pronounced in septic shock than in cardiogenic shock.

After the infusion of calcium gluconate was stopped haemodynamic variables returned to pre-infusion values within 20–40 min. Infusion over 6 h in six patients did not provide evidence of tolerance to the effect of calcium.

The haemodynamic data of one 57-yr-old patient in refractory septic shock despite treatment with adrenaline, noradrenaline and angiotensin are shown in figure 5. The administration of calcium gluconate 20 mmol h^{-1} resulted in an increased mean aortic pressure and augmented cardiac output, despite a reduction in use of vasopressor drugs. Calcium infusion was stopped in this patient when the serum concentrations of calcium became available (total calcium after 6 h of calcium infusion, 4.4 mmol litre^{-1}; ionized Ca^{2+} 2.6 mmol litre^{-1}). Cessation of infusion of calcium was followed by a decrease in aortic pressure to the initial values. After the infusion was restarted, pressures recovered to previous values (fig. 5). The increased plasma concentrations of calcium

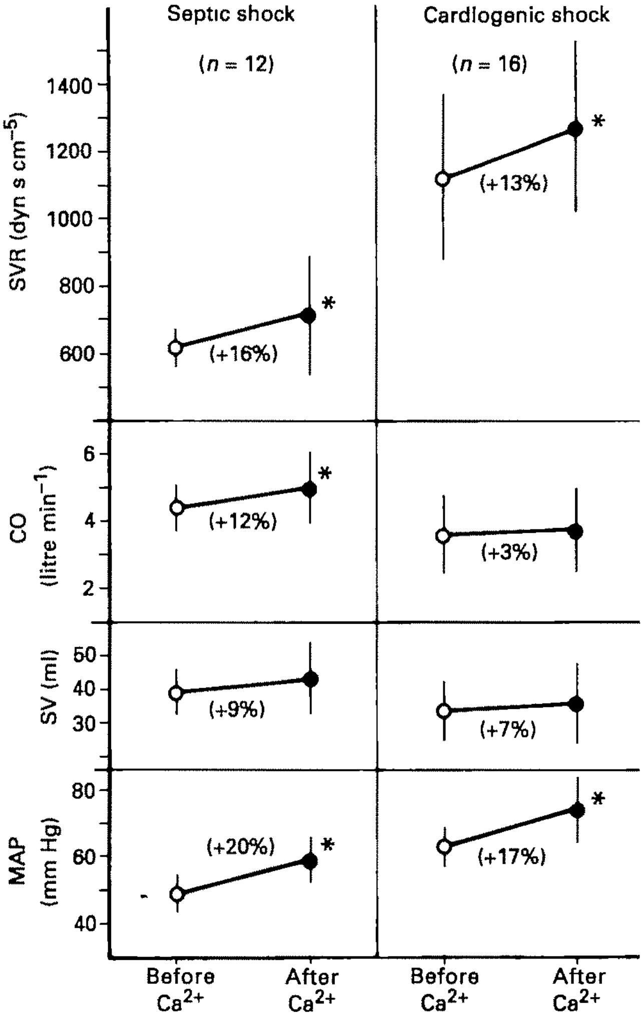

FIG. 4. Haemodynamic effects of calcium in patients with dilated cardiomyopathy and either cardiogenic or septic shock. Haemodynamic measurements (mean, SD) were performed before (○) and after (●) constant infusion of Ca^{2+} 20 mmol h^{-1} for 30 min. *$P < 0.05$.

(> 4 mmol $litre^{-1}$) were seen repeatedly without apparent associated arrhythmias or haemodynamic problems.

In summary, we found that calcium supplementation proved to be effective and safe in patients with cardiogenic and septic shock, as has been reported previously [5, 8, 11]. We did not observe tolerance or arrhythmias. This form of treatment may be suitable for patients awaiting cardiac transplantation or operation to eliminate the septic origin. We were surprised to observe that calcium appeared to be effective, even in the presence of other positive inotropic and vasopressive agents such as dopamine, dobutamine, noradrenaline, adrenaline and digitalis. Further investigations are needed to evaluate the therapeutic value of calcium in end-stage heart failure, but these data do suggest that calcium increases cardiac output and systemic pressures if infused constantly.

CALCIUM SUPPLEMENTATION IN CARDIAC ARREST

Cardiac arrest is rather different from the above mentioned conditions, and may be caused by severe arrhythmias (ventricular tachycardia or ventricular fibrillation), asystole or electromechanical dissociation (EMD), and conditions such as

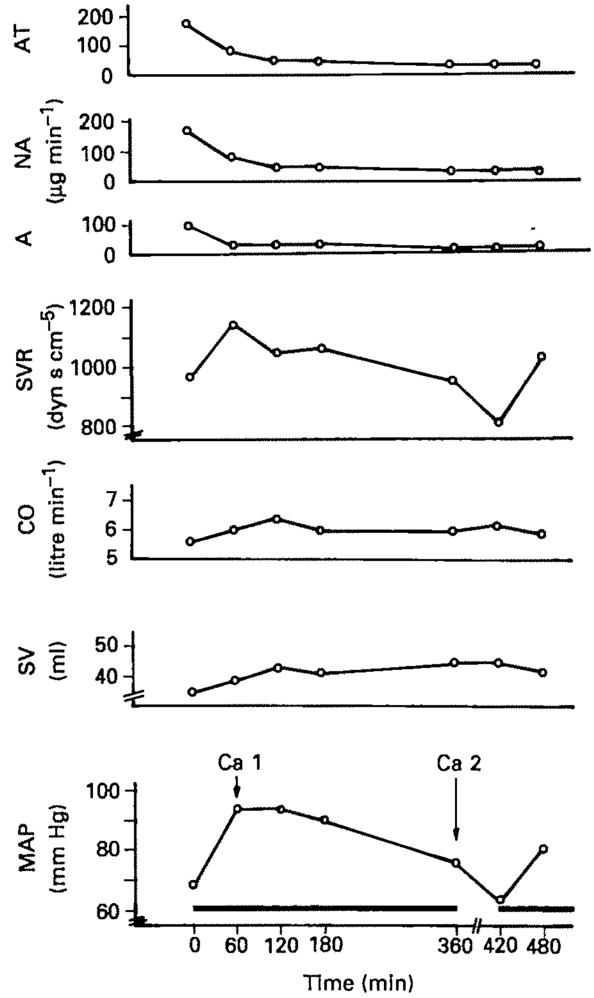

FIG. 5. Haemodynamic effects of calcium in a 57-yr-old female patient with septic shock. Calcium 20 mmol h^{-1} was infused (——) over 6 h and again after it had been stopped for 60 min. Serum concentrations of calcium (total: ionized) were 1.95: 1.6 mmol litre^{-1} at Ca 1 and 4.4: 2.6 mmol litre^{-1} at Ca 2. A = Adrenaline; NA = noradrenaline; AT = angiotensin.

cardiac tamponade, tension pneumothorax, right ventricular infarction, pulmonary embolism, volume depletion and asphyxia (experimental model). At the time of starting resuscitation procedures, the cause of cardiac arrest usually is uncertain. If asystole is present, previous ventricular fibrillation or bradycardia may have degenerated into asystole by the time the patient is first seen by the physician. Thus, at least in an "out-of-hospital" event, the true origin of cardiac arrest is often unclear.

Animal experiments in most cases differ from the human clinical situation in several ways [1, 2, 13]: (a) the animal is anaesthetized first; (b) usually, high concentrations of potassium chloride are used to produce cardiac arrest after electrically-induced ventricular fibrillation; (c) in asphyxiated dogs the subsequent EMD is not comparable to that in humans; (d) laboratory animals are usually young, without underlying heart disease. Because of these differences, the efficacy of calcium in cardiac arrest should be judged on the basis of clinical reports.

Two independent groups have investigated this problem in detail. Steuven and colleagues [26] studied 129 patients presenting initially in asystole. Only eight of 105 patients who received calcium 0.5–1.0 g were resuscitated successfully, compared with eight of 24 patients who had not received calcium. This retrospective investigation was similar in outcome to a study in 81 patients presenting initially in EMD. Again, more patients were resuscitated successfully (return of heart rate and arterial pressure) when additional calcium was not given. No patient who received calcium was discharged alive from the hospital. Harrison and Amey [9] conducted a similar, uncontrolled and retrospective study based on hospital records over a 2-year period. Calcium 1 g was given i.v. for ventricular fibrillation, asystole and EMD; it was ineffective in all patients presenting with ventricular fibrillation, and only 27 patients with EMD responded. There were only three long-term survivors. Adverse rhythm or rate changes were not recorded. As these studies were neither randomized nor controlled, they are not amenable to analysis in greater detail.

The only randomized, prospective, blind study of this problem was conducted by Stueven and colleagues [27] in a pre-hospital setting. Only patients who had received adrenaline and bicarbonate and were refractory to this treatment were entered to the study. Ninety patients presented with refractory EMD. Eight of 48 receiving calcium i.v. (5 ml of a 10% solution of calcium chloride (500 mg)) were resuscitated successfully, compared with only two of 42 receiving saline. It was noted that patients with EMD and a wide QRS complex (> 0.12 s) responded more favourably to calcium (eight of 39 patients, compared with one of 38 not receiving calcium). Although calcium seemed to be effective in these patients (EMD with QRS > 0.12 s), only one patient who was successfully resuscitated was discharged from the hospital alive. These data suggest that there may be a subset of patients who will "most likely benefit from the use of calcium" [27]: those with EMD and a QRS complex > 0.12 s. All other previously indicated causes of cardiac arrest (ventricular fibrillation or asystole) do not seem to benefit from the use of calcium [10, 16, 19, 22, 29].

INDICATIONS FOR CALCIUM IN RESUSCITATION

Hypocalcaemia

Although hypocalcaemia may not be as common in these patients as previously thought [4, 6, 21, 28, 30, 32], it seems prudent to provide supplementary calcium in proven hypocalcaemic cardiac arrest [20].

Hyperkalaemia and severe cardiac arrhythmias

Increased serum concentrations of potassium are associated with a broad QRS complex, prolongation of the P–Q interval, widening of the P-wave and a tall, peaked T-wave. If the concentration of potassium is increased rapidly, ventricular fibrillation is seen at small concentrations of potassium than after slowly developing hyperkalaemia. It has been shown experimentally that calcium can reverse the arrhythmic effects of hyperkalaemia. However, as it does not decrease the serum concentration of potassium, it can be expected to be of only temporary benefit.

Overdosage of calcium antagonists

It has been shown in patients with verapamil intoxication and in experimental animals that calcium supplementation is the effective treatment of choice [12, 17].

After cardiopulmonary bypass

Many surgeons and anaesthetists believe that some patients leaving cardiopulmonary bypass need supplementary calcium. This may be because of effects of the cardioplegic solution (large concentration of potassium), the use of citrate or the degree of ionization of Ca^{2+} in the blood while the patient is on cardiopulmonary bypass. This situation is unique, and may differ from resuscitation procedures [7, 14, 15].

EMD with wide QRS

At present, the recommendation to give calcium is based on one study (see above), which has been criticized on statistical grounds [25]. As the prognosis of such patients is often very poor, and there is no other established form of treatment, it may be argued that calcium should be administered in this situation. However, there does not seem to be a place for calcium in asystole or in ventricular fibrillation.

HOW TO GIVE CALCIUM?

Total calcium in the blood (approximately 2.5 mmol $litre^{-1}$) exists as plasma protein-bound calcium and free (ionized) calcium (approximately 50% of total calcium). Calcium may be administered as calcium chloride (10% solution, 680 mmol $litre^{-1}$) or calcium gluconate (10% solution, 225 mmol $litre^{-1}$). Calcium is administered usually as 10% calcium chloride 5–10 ml infused over 10 min. This certainly increases the serum concentration of calcium, which may not be very dangerous because reports of arrhythmia are rare. We favour a slow infusion of calcium over a period of 20–30 min. The rapid infusion of calcium, especially in patients receiving digitalis, may be dangerous (severe arrhythmias, asystole).

SUMMARY

Calcium ions are essential for myocardial excitation–contraction coupling and for increasing contractility of the heart. Because of these physiological effects, use of calcium has been recommended in the treatment of electromechanical dissociation, asystole and ventricular fibrillation. Recently, however, the use of calcium during cardiac arrest has come into dispute, as there are no controlled clinical trials supporting a favourable haemodynamic effect. It has rather been suggested that, in resuscitation, calcium may have detrimental effects.

In order to evaluate the role of calcium in cardiopulmonary resuscitation, it is important to know the serum concentrations of calcium and the haemodynamic effects in this situation. Measurements in some patients with cardiac arrest have demonstrated that severe hypocalcaemia may not be uncommon. In these patients, calcium may augment myocardial contractility, decrease intracardiac filling pressures and increase mean arterial pressure. At present, the more or less established indications for use of calcium during cardiopulmonary resuscitation are in treating patients with proven hypocalcaemia, hyperkalaemia, calcium channel blocker overdose and, possibly, electromechanical dissociation combined with a wide QRS complex. There is no good evidence

supporting the routine use of calcium in resuscitation.

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FLUIDS FOR RESUSCITATION

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The vast majority of acutely ill patients admitted into the intensive care unit require volume expansion at some stage of their stay. Patients suffering from haemorrhage, extended trauma or severe dehydration are obvious candidates. Septic, traumatized and even postoperative patients also develop exudation of plasma into the inflamed areas. Patients with sepsis may develop generalized alterations of the endothelial barrier, resulting in diffuse capillary leak and generalized oedema. This accumulation of extravascular fluid may contribute to the development of cellular hypoxia and multiple organ failure. Treatment with positive pressure ventilation decreases venous return to the heart, so that fluid therapy is often indicated to stabilize the haemodynamic status despite the usually increased central venous pressure in these conditions. Thus fluid deficits can be present in the absence of obvious losses, and even in presence of oedema. Their correction is, however, important to maintain oxygen transport to all tissues [49].

ASSESSMENT OF FLUID REQUIREMENTS

Global dehydration can be recognized relatively easily by clinical examination of the teguments, and can be confirmed by estimations of simple biochemical quantities such as blood concentration of urea, osmolarity or serum sodium concentration. Similarly, the presence of oedema indicates an increased water content of the body; however, the presence of oedema does not rule out some plasma volume depletion. The clinical signs of hypovolaemia are not very reliable. They may include an increased heart rate and a reduced arterial pressure, but neither of these changes is specific or sensitive. Changes in pulse pressure or postural changes in arterial pressure may be earlier indicators of hypovolaemia. A slow capillary filling time in the cutaneous extremities may represent another valuable sign of reduced perfusion. A reduction in urine output and, in particular, an increase in urine osmolarity and a reduced natriuresis may reflect a reduction in kidney perfusion; however, this may result from cardiocirculatory factors other than hypovolaemia. The cardiac filling pressure may be influenced by several factors other than blood volume, including those influencing cardiac performance, vascular compliance and intrathoracic pressure. Ultimately, the cardiovascular response to a trial of fluid administration may represent the best clinical assessment of the patient's circulatory blood volume.

The fluid challenge technique, initially proposed by Weil and Henning [65] represents a standardized method for testing the cardiovascular response while minimizing the risk of development of pulmonary oedema. Before starting the infusion, three types of information are required. First, the type of fluid to be infused must be defined; this aspect will be discussed later. Second, the rate of the infusion pump must be defined according to the degree of suspicion of hypovolaemia and the expected response to fluid infusion. Third, the criteria for discontinuation of the fluid infusion must be defined; satisfaction of any one of three criteria terminates the fluid challenge: (i) the resolution of the problem (for instance, the heart rate decreases to less than 120 beat min^{-1}; arterial pressure is satisfactory; urine output is acceptable); (ii) a maximal filling pressure (for example, central venous pressure reaches 13 mm Hg); (iii) fluid challenge rules:

KEY WORDS
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TABLE I. *Rules of the fluid challenge technique. PAOP = Pulmonary artery balloon-occluded pressure; RAP = right atrial pressure*

Change in 10 min (PAOP or RAP)	Action
< 3 mm Hg	Continue infusion
3–5 mm Hg	Interrupt infusion (re-evaluate 10 min later)
> 5 mm Hg	Stop infusion

standard rules, based on measurements of cardiac filling pressure repeated every 10 min, are proposed in table I.

TYPES OF I.V. FLUID

Crystalloids

Glucose solutions essentially provide free water, because glucose is metabolized rapidly. As the total body water represents about 60% of body weight and plasma volume about 5%, less than 10% of an administered solution of glucose remains in the vascular space. Therefore, glucose solutions are ineffective plasma expanders.

Saline solutions are distributed into the extracellular space, which represents about 33% of total body water. Thus approximately 25% of the normal saline infused remains in the vascular space. The administration of normal saline may result in hypernatraemia and hyperchloraemic acidosis. Therefore, Ringer's lactate solution, which has a slightly smaller sodium content but which contains sodium lactate (metabolized to bicarbonate), is often preferred when massive crystalloid infusions are administered. Half-normal saline solutions may be indicated in dehydration with hypernatraemia, but are poor plasma expanders.

Colloids

The rate of passage of fluid across the capillary membrane (Q) is governed by the Starling relationship:

$$Q = K\text{fc}[\text{Pmv} - \text{Ppmv}) - \sigma(\text{COPmv} - \text{COPpmv})]$$

where Kfc = coefficient of filtration defining the physicochemical characteristics of the capillary membrane; σ = reflection coefficient defining the permeability characteristics of the membrane to large molecules; P = hydrostatic pressure and COP = colloid osmotic pressures of the microvascular (mv) and the perimicrovascular (pmv) spaces, respectively. The COPmv is attributable chiefly to albumin, which has a molecular weight of 69000. The normal COPmv is about 25 mm Hg, but in critically ill patients a COP value of about 20 mm Hg is acceptable.

Natural colloids include 5% and 25% albumin solutions. The 5% solution remains largely within the vascular space when the capillary membrane is intact, so that it represents a natural plasma expander. The hyperoncotic 25% solution pulls fluid from the interstitial space, so that it may be preferred in oedematous patients. Fresh frozen plasma may be indicated in patients with coagulation abnormalities, but should not otherwise be considered as a plasma expander because it can be a vector of infectious agents.

Colloids vs *Crystalloids Controversy*

Pulmonary implications

For many years the colloids *vs* crystalloids controversy focused on the formation of pulmonary oedema. As the pulmonary artery balloon-occluded pressure (PAOP) reflects the capillary microvascular pressure (Pmv) and is accessible like the plasma COP, some authorities have shown that the COP–PAOP pressure gradient may indicate the risk of development of pulmonary oedema in the critically ill [43, 66]. It is clear, however, that of the two factors, the PAOP is by far the most important. Moreover, the lung is relatively well protected against the development of pulmonary oedema by its very efficient lymphatic system. The numerous clinical studies comparing the effects of the type of i.v. solutions on the incidence and the severity of respiratory complications failed to demonstrate convincingly a significant difference between the benefits conferred by colloids and crystalloids.

To understand the influence of fluid type on the development of pulmonary oedema, we will consider normal and diseased lungs in turn.

Normal lungs. The Starling equation presented above indicates that, for any given hydrostatic pressure, a reduction in COPmv increases the rate of fluid egress into the interstitium. Several experimental studies indicated that hypo-oncocity is not associated with the development of pulmonary oedema, provided that Pmv remains normal, because lymphatic flow increases simultaneously [24, 71]. This observation is consistent with the absence of pulmonary oedema in patients with chronic hypoalbuminaemia related, for instance, to cirrhosis or nephrotic syndrome.

If Pmv is increased, COPmv must represent a protective mechanism against the development of pulmonary oedema. In their classical experiment, Guyton and Lindsey [15] used plasmapheresis to reduce the plasma proteins of dogs by 50 % before increasing their Pmv. In these hypo-oncotic conditions, the value of critical Pmv above which oedema developed was also reduced by 50 % from 25 to 12 mm Hg. Also in dogs made hypoalbuminaemic by plasmapheresis, Rackow and co-workers [45] compared the effects of saline, albumin and hydroxyethylstarch infused so as to maintain PAOP at 15 mm Hg. As expected, the total amount of fluids required was about three times larger when saline was infused. In crystalloid-treated animals, the extravascular water content was also significantly larger than that in colloid-treated animals. Using the awake sheep model in which lymph can be collected, Wareing and colleagues [62] demonstrated that, in the presence of increased Pmv, saline administration increased the lymphatic flow more than did a colloid solution. These experiments indicate, therefore, that in the presence of an increased Pmv, the degree of pulmonary oedema formation is greater when COPmv is reduced. The clinical applicability of these observations is not straightforward, since administration of colloid produces a larger increase in intravascular hydrostatic pressure. Therefore, in the stable patient with hypoproteinaemia, colloid administration might not be indicated. Patients with cirrhosis or nephrotic syndrome provide typical examples. If colloid solutions are administered to such patients despite the risk of overloading, the rate of infusion should be low. Simultaneous diuretic therapy may avoid any increase in Pmv. In a patient requiring i.v. fluids, a colloid solution may be preferred in order that COPmv may be preserved as a protective factor.

Pathological lungs. Acute respiratory failure is frequently associated with an alteration of the capillary membrane, and the consequent reduction of the reflection coefficient, σ, reduces the influence of COP on fluid egress across the capillary membrane. In an extreme situation, the coefficient σ could be reduced to zero, so that the effects of COP would be entirely abolished. Using a canine model in which vascular permeability was altered by the administration of alpha-naphthylurea, Rutili, Parker and Taylor [49] observed similar increases in lymphatic flow and extravascular lung water after administration of either colloids or crystalloids. Similar observations were made by other investigators [35, 47]. Using a model of pulmonary oedema induced by fibrin microembolization in dogs, Schaeffer and colleagues [50] titrated the administration of colloids and crystalloids in order to maintain the left atrial pressure constant at 15 mm Hg, and observed an equivalent formation of pulmonary oedema with the two treatment regimens. In dogs, Prewitt, McCarthy and Wood [39] observed that the formation of oleic acid-induced pulmonary oedema was lessened by a decrease in Pmv, but not by an increase in plasma COP. Finally, in a complex dog model of haemorrhagic shock combined with oleic acid-induced pulmonary oedema, Pearl and co-workers [37] found that the type of fluid did not influence gas exchange, lung compliance or extravascular lung water. These studies confirm that, when the capillary permeability of lung capillaries is altered, colloid solutions do not appear to exert any protective effect. Again, the value of Pmv plays a more important role than that of plasma COP in the formation of the pulmonary oedema.

Systemic implications

Since a greater proportion of a colloid solution remains in the intravascular space, a smaller volume is required to achieve the same cardiovascular effect. Many studies have indicated that about three times more fluid is required for resuscitation when crystalloid rather than colloid solutions are administered. This has two important consequences. First, the fluid resuscitation may be more easily achieved with colloids than with crystalloids. Hauser and co-workers [18] observed that colloid solutions restore oxygen transport indices more effectively than crystalloid solutions in hypovolaemic patients. Second, even though there may be no difference in the formation of pulmonary oedema, there must be a difference in the formation of systemic oedema. It remains reasonable to assume that the formation of interstitial oedema may reduce the diffusion of oxygen to the tissues. It may also hinder the healing processes in inflamed tissues. However, differences in terms of morbidity and mortality have not been demonstrated clearly. A meta-analysis of these studies [58] suggested a decreased

TABLE II. *Comparison of crystalloids and colloids*

	Crystalloids	Colloids
Space distribution	Extracellular	Primarily intravascular
Haemodynamic effects	Transient	Rapid and sustained
Amount required	More (three times)	Less (three times)
Risks	Oedema formation by a decrease in COPmv	Oedema formation by an increase in Pmv
Cost	Inexpensive	Expensive

TABLE III. *Comparison of the principal synthetic colloids*

			Hydroxyethylstarch	
	Gelatins	Dextran 70	Hetastarch	Pentastarch
Usual concentration (%)	3–3.5	6	6	6–10
Mean mol. wt	35000	70000	450000	200–260000
Degree of substitution	—	—	0.7	0.4–0.6
Initial volume effect (%)	80	120	100	100–140
Plasma half-life (h)	2–3	6	6–8	3–6
Total elimination	Very rapid	Rapid	Very protracted	Protracted
Anaphylactoid reactions	Rare	Possible	Rare	Rare
Coagulopathies	Rare	Possible	Rare	Rare
Other effects	—	Difficult crossmatching	Hyperamylasemia	Hyperamylasemia

mortality when crystalloid solutions were used in traumatized patients, and increased mortality when colloid solutions were used in non-traumatized patients. These data emphasize that the type of i.v. fluid used represents only one of many factors influencing morbidity and mortality in critically ill patients. Probably, the amount is more important than the type of fluid administered.

Since critically ill patients often develop capillary membrane abnormalities, the egress of larger molecules into the extravascular spaces may also increase COPpmv and thus limit the effects of exogenous colloids on the maintenance of blood volume. Furthermore, it has been argued that the extravasation of colloid solutions might worsen interstitial oedema and hinder its resorption. The arguments favouring this latter hypothesis are, however, lacking.

Table II summarizes the relative advantages and disadvantages of colloid and crystalloid fluids.

Synthetic Colloids

The major obstacle to the use of colloids remains their cost. However, the development of synthetic colloids has largely alleviated this problem. Table III presents the principal characteristics of the synthetic colloids currently available. Among these, the gelatins are the least expensive, but also those with the shortest cardiovascular effects. The dextrans are better plasma expanders, but their use may be associated with several, although infrequent, problems; these include coagulation abnormalities, impaired blood crossmatching and sometimes severe allergic reactions. Hydroxyethylstarches (HES) are derivatives of amylopectin with more limited secondary effects. In contrast to dextrans which have a linear molecular structure, HES has a spherical structure. Tissue accumulation of HES in the reticulo-endothelial system has been of concern, but does not appear to have deleterious consequences. By forming an amylase–starch complex, HES solutions can increase serum concentrations of amylase to more than twice the normal values over a period of several days [6].

There are several types of HES solutions, characterized by their molecular weight (mol. wt) and degree of substitution (the number of hydroxyethyl groups per molecule of glucose). It is important to note, however, that all HES solutions have a heterogenous composition, so that their mol. wt is reported as either the number average value (arithmetic mean of the mol. wt) or as the weighted average value (sum of the number of HES molecules at each mol. wt divided by the

TABLE IV. *Advantages and limitations of hypertonic solutions*

Advantages	Limitations
Excellent volume effects	Hypernatraemia/osmolarity
Improved cardiac function	Cellular dehydration
Increased myocardial blood flow	Brain shrinkage
Increased diuresis	Hypokalaemia
Reduced weight gain	Fluid overload
Reduced intracranial pressure	Thrombophlebitis
Reduced incidence of ileus(?)	Worsening of uncontrolled haemorrhage

total weight of all HES molecules). The first developed solution, hetastarch, has a large mean mol. wt, and a high degree of substitution. This solution has been shown to be as effective as 5% albumin for volume expansion in patients [26, 32, 42]. More recently, other solutions have been proposed with a lower mol. wt and a lower degree of substitution: these are more rapidly degraded and eliminated. The smaller HES particles are usually not phagocytosed, so that about 90% is eliminated within 24 h and even trace amounts are undetectable within 7 days [31]. These solutions may be preferred for acute haemodilution to limit blood transfusions in surgical patients or to improve capillary blood flow in some microvascular disorders. They also have a better volume effect, especially when a 10% concentration is used [22]. The administration of these solutions has been found safe and effective in various conditions including sepsis [44], burns [63] or after cardiac surgery [27]. These solutions might be retained better in the circulation in capillary leak syndromes [64], and might reduce the reperfusion injury [72].

Hypertonic Solutions

Hyperosmolar solutions have been used for many years. In 1926, Silbert [54] reported an improvement in local blood flow in patients with thromboangiitis obliterans. In the 1970s, Monafo, Chuntrasaleul and Ayvazian [33] administered hypertonic solutions to burned patients in order to limit fluid losses. Hypertonic solutions were also used effectively in patients after vascular surgery in whom the fluid losses are notoriously large [2, 53]. More recently, there has been interest in the use of these solutions in the pre-admission management of patients with multiple injuries [19, 30].

In experimental studies of traumatic shock, hypertonic solutions have been shown to be superior to normotonic solutions in terms of restoration of arterial pressure, diuresis, cardiac output, oxygen transport and oxygen consumption, and ultimate survival (table IV) [5, 25, 38, 55, 57, 59]. Similar observations have been made in experimental septic shock [29]. In addition to the larger volume effect, other factors can contribute to the better haemodynamic effects of hypertonic solutions. The effects of hyperosmolarity and hypernatraemia on myocardial contractility are complex and still controversial. Myocardial contractility has been found sometimes to increase [67] and sometimes to decrease [23]. These diverging observations may be explained by differences in the type and degree of hyperosmolarity, and also the model used. In particular, a catecholamine response can compensate for intrinsic myocardial depression [67]. Hypertonic solutions may also increase the myocardial availability of calcium [3]. Cardiac function may also be improved by the direct vasodilating effects of hyperosmolar solutions. A reflex vagal mechanism provoked by the passage of hyperosmolar solutions through the lungs may also play a role [28], and lung denervation abolishes the beneficial cardiovascular effects [70]. Release of arginine vasopressin may be involved in the increase in arterial pressure [17]. However, in patients after surgery, the hormonal response has been found to be reduced [8].

In addition to the global cardiovascular improvement, there might be beneficial local factors. Hyperosmolarity induced by mannitol has been shown to protect the myocardium from ischaemic damage [51, 68]. The suggested mechanisms are a sustained improvement in coronary blood flow and reversal of myocardial oedema. The improvement in coronary blood supply may be the result of a dilating effect on large arterial conductance vessels, similar to that produced by nitroglycerin, in addition to a more distal effect on the microvascular circulation [61]. Hypertonic dextran solutions might also have a protective action on the myocardium by a scavenging effect of the colloid on toxic oxygen metabolites [4]. Direct cellular protective mechanisms have also been suggested [34]. Nevertheless, hypertonic solutions do not seem to improve the peripheral oxygen extraction capabilities of the tissues [46].

The cardiovascular effects of hyperosmotic solutions are usually transient, but their cardiovascular effects may be prolonged by the administration of hypertonic/hyperoncotic solutions. Thus the global volume effect of the hyperosmolar solution may favour the plasma space. Experimentally, hypertonic saline–dextran improved early haemodynamic and metabolic responses and decreased the total volume requirements for resuscitation [25]. A bolus injection of hypertonic/hyperoncotic fluid also improves survival from severe haemorrhagic shock in dogs [60]. In experimental septic shock also, we observed that hypertonic HES improved haemodynamic status better than normotonic HES, although the changes appeared transient [1]. In an experimental model of pancreatitis, hypertonic saline–dextran was found to restore cardiac function better than Ringer's lactate [20].

The administration of hypertonic solutions might also exert protective effects on pulmonary function. As the fluid retention is less significant and urine output is greater, the degree of post-resuscitation pulmonary oedema might be reduced. In experimental pancreatitis, Horton and colleagues [20] reported a lesser degree of pulmonary hypertension and pulmonary oedema in animals treated with hypertonic colloids. Using a model of acute haemorrhage, Cone and colleagues [7] observed a better late pulmonary function when hypertonic solutions were used.

Clinical studies on these solutions remain scarce. In the prehospital resuscitation of severely injured patients, Holcroft and colleagues [19] observed a better arterial pressure response and an improved survival with 7.5% saline–dextran 70 solutions than with lactated Ringer's solution. Other preliminary studies stressed the lack of complications associated with this type of solution [30].

The place of hypertonic solutions in the treatment of burns is not settled. Early clinical studies were encouraging [33]. In experimental burn injury, Horton's group [21] reported that hypertonic saline–dextran was the optimal fluid for maintaining cardiac function and maximized the chances of survival. In another experimental study in sheep [36], hypertonic saline–dextran was only transiently effective, and this was attributed to the sustained increase in vascular permeability and protracted plasma leakage. A prospective, randomized study of hypertonic sodium lactate compared with lactated Ringer's solution for resuscitation in patients with burn shock did not reveal any significant difference between the two treatment regimens [13]. The authors suggested the possibility that their policy of early and aggressive enteral feeding may have negated the effects of hypertonic solutions on the fluid balance of these patients [13].

Hypertonic solutions may have both hazardous and favourable effects on brain function. Hypernatraemia and hyperosmolarity may provoke cellular dehydration. However, the reduction in fluid extravasation may be expected to limit the formation of vasogenic oedema. In normal animals, isovolaemic haemodilution with hypertonic lactated Ringer's solution increases cerebral blood flow, but reduces the development of oedema in the brain (as in other tissues) [56]. In experimental animals, hypertonic solutions limit the transient increase in intracranial pressure (ICP) which usually follows the administration of i.v. fluids to patients suffering from haemorrhagic [10, 14, 52] or septic [40] shock. This difference in increase in ICP was observed after both short-term and prolonged infusions [52]. The increase in ICP was also blunted in experimental head trauma [69, 73] or in a model combining haemorrhage and an extradural mass [9]. However, an electrophysiological study [16] reported a better return of the electrocortical function (as assessed by somatosensory evoked potentials) after treatment with 6% hetastarch than after hypertonic saline–dextran. This was related to a poorer restoration of cerebral perfusion pressure in relation to the reduction in vascular tone induced by the hyperosmotic solution.

The beneficial haemodynamic effects of hypertonic solutions must be weighed against their potentially deleterious effects. The sodium load may result in a rapid increase in the serum concentration of sodium and osmolarity which, in turn, may provoke cerebral oedema; rapid replacement of sodium may be particularly hazardous in hyponatraemic patients. Local disruption of the blood–brain barrier may draw water from normal tissues and thus expand an intracranial lesion. Development of hypokalaemia is commonly observed, and is probably caused by enhanced loss of potassium in the urine; consequently, cardiac arrhythmias may sometimes occur, and prudence is thus particularly warranted in patients receiving digitalis therapy. The risks of fluid overload present a real hazard to patients with heart failure. The solutions are irritant and may induce phlebitis; however, an experimental study suggested that the peripheral infusion of hypertonic colloids is both safe and effective [16]. Small boluses of saturated saline–dextran solutions may induce haemolysis at the point of injection [48]. Finally, the rapid haemodynamic improvement with restoration of arterial pressure may lead to uncontrolled bleeding. In a rat model of uncontrolled haemorrhagic shock, Gross and co-workers [11, 12, 41] observed that hyperosmotic solutions increased blood losses from the injured vessels, with reduced survival.

Thus hypertonic solutions are still an investigative form of therapy that necessitates further study before it can be applied to patients.

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POTASSIUM IN THE PERIOPERATIVE PERIOD

R. S. VAUGHAN

Potassium ions play a vital role at a cellular level. These ions are actively transported into cells, causing an electrical imbalance and a build up of potential energy. When this energy is released following correct stimulation, the cells perform their designated functions. When these functions relate mainly to the heart and skeletal muscles, nerve and renal activity, the importance of potassium in cell function becomes very clear indeed.

The excitability of the cells is proportional to the ratio of intracellular to extracellular potassium concentrations [8, 29]. Consequently, any variations in this ratio will affect cellular function, result in dysfunction of excitable cell membranes and cause the signs and symptoms [39] that are associated with imbalances of potassium concentration.

NORMAL POTASSIUM HOMEOSTASIS

The average normal body intake of potassium is about 1 mmol kg^{-1} day^{-1}. Most of the potassium ingested is absorbed in the small intestines and redistributed around the body, where the main reservoir is the skeletal muscles. Approximately 90% of the total amount of potassium absorbed each day is excreted by the kidney, mainly at the distal convoluted tubules, in exchange for either sodium or hydrogen ions. This exchange is influenced predominantly by aldosterone [29].

Excretion of aldosterone from the adrenal glands is directly proportional to the serum concentration of potassium. A high concentration will lead to an increased secretion of aldosterone, and *vice versa*. This relationship is unaffected by sodium balance and renin concentrations. Although the function of aldosterone is related mainly to the renal aspects of potassium homeostasis, it has a secondary action in that it increases the uptake of potassium ions by skeletal cells [7].

There are also extrarenal mechanisms involved in the control of the serum concentration of potassium. Insulin induces potassium to enter the cells; this is independent of glucose uptake. Further, if the serum concentration of potassium increases greatly, additional insulin may be secreted from the pancreas. There is also evidence that there is a critical minimum concentration of insulin required for the normal uptake of potassium by cells [7].

The liver also has a modulating action. As the portal circulation drains into the liver, increased concentrations of insulin can have a significant effect upon subsequent serum concentration of potassium, causing potassium ions to move into the liver cells thus reducing the serum concentration. This relationship between the pancreas, the portal circulation and the liver provides one of the important mechanisms involved in the normal daily control of serum potassium [16].

It is not surprising, therefore, that occasionally after liver transplantation, there may be a significant increase in the serum concentration of potassium after the transplanted organ has been connected to the recipient's circulation [16]. However, recent developments in technique have enabled liver surgery to proceed without such an increase in serum potassium [12].

Membranes containing the enzyme sodium–potassium ATPase are also important modulators of potassium balance. This enzyme pumps potassium into the cell and sodium out [33]. There are several factors which can affect the action of this enzyme. One of the most important is the activity of the sympathetic nervous system [27].

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Beta-adrenergic agonists and α-adrenergic inhibitors encourage potassium ions to enter the cell; β-antagonists and α-agonists have the reverse action. It has been suggested also that the serum concentration of magnesium affects the action of sodium–potassium ATPase.

Finally, the plasma pH also influences potassium homeostasis. During episodes of acidosis, hydrogen ions enter the cell and are exchanged for potassium ions, causing an increase in serum concentration of potassium. During an alkalotic period, the reverse occurs [30].

POTASSIUM IMBALANCE

There are two main clinical conditions associated with potassium imbalance which affect the anaesthetist, namely hyperkalaemia and hypokalaemia. However, whichever clinical condition the anaesthetist faces, *acute* changes in potassium concentrations present the greatest hazards. Chronic changes are far less dangerous and are managed more easily.

Hypokalaemia

It would appear that the clinical picture associated with hypokalaemia does not usually occur until the serum concentration of potassium decreases to less than 3.5 mmol litre^{-1}. Thereafter, the electrical activity of the heart may alter and the heart become susceptible to arrhythmias, and in particular to the effects of digitalis [18]. The classical ECG leads may show S–T segment depression, flattened T-waves, U-waves, tachycardia and eventually ectopic beats. In addition, the compensatory mechanisms which normally follow the Valsalva manoeuvre [39] are depressed also. Thus postural and perioperative hypotension can occur and may need additional therapy for correction.

Skeletal muscle weakness may also occur and this could, in the long term, be followed by the release of muscle protein into the blood. These complications may cause early respiratory and long-term renal failures. Rarely, when the serum concentration of potassium decreases to very small values, only the diaphragm and the cranial nerves function: this can present as dyspnoea, with the so called fish mouth breathing picture [39]. The gastrointestinal system is also affected, with a generalized decrease in function. This delays gastric emptying and causes a decrease in the release of insulin.

The major cause of hypokalaemia is loss of potassium from the body. Vomiting and diarrhoea cause considerable losses. Renal losses occur following excessive diuretic therapy without additional potassium therapy, with the loop diuretics producing a greater loss than the potassium sparing diuretics; diabetes mellitus and alkalosis may have the same effect. Hypokalaemia occurring in patients receiving β_2-adrenergic agonists, xanthines and steroids has been recorded with increasing frequency [6]. Of the 26 reports received by the Committee on Safety of Medicines, four were associated with cardiac arrest. Rarer causes of hypokalaemia include Cushings syndrome, nephrosis and cirrhosis.

The main question that the anaesthetist needs to ask is: "*What is the minimum safe recommended serum concentration of potassium at which routine or emergency anaesthesia may be undertaken?*" The general consensus of opinion used to be about 3.5 mmol litre^{-1}, although there is now evidence to suggest that 2.5 mmol litre^{-1} may be acceptable [38]. Despite this evidence, most anaesthetists faced with a hypokalaemic patient in the preoperative period would set up an infusion containing potassium. However, this concept does not find universal support, as Hirsch and colleagues [13] found no major problems in patients with a serum concentration of potassium less than 3 mmol litre^{-1}. The problems that did arise, namely cardiac irregularities, were associated more with previous congestive cardiac failure or long-term digoxin therapy.

The recommended maximum rates of infusion of potassium are 10–20 mmol h^{-1}, with a maximum of 500 mmol 24 h^{-1}. Further, the potassium should be infused from a pre-set pumping device and should enter the blood stream utilizing a "piggy-back" technique. Concentrated solutions of potassium given directly into a peripheral vein may cause local reactions, pain and ultimately phlebothrombosis. Large concentrations have also caused cardiac arrest [40]. It should be noted also that it may require up to 2 days to replenish body losses completely.

Hyperkalaemia

The clinical indications of hyperkalaemia are a decrease in the excitability of cardiac muscle, weakness of skeletal muscle and an increase in the release of insulin. The most dangerous effect of hyperkalaemia is on the myocardium. There would appear to be a threshold concentration of approximately 7 mmol litre^{-1} at which arrhythmias start to occur [35]. If the potassium concentration increases rapidly, there is an added risk of decreased cardiac output, ventricular fibrillation or asystole. Increasing concentrations are associated with characteristic sequential changes on the ECG: appearance of tall, peaked T-waves, followed by absence of P- and diminished amplitude of the R-waves, a widened QRS complex terminating in a biphasic QRST. Ventricular fibrillation or asystole may then occur.

The major causes of preoperative hyperkalaemia are renal failure and iatrogenic events. The latter have included accidental potassium overdose [40], the infusion of triple strength plasma [41] and the transfusion of outdated blood [21] with a concentration of potassium greater than 30 mmol litre^{-1}. More unusual causes include pseudohyperkalaemia and the changes which follow tissue damage and hypoxia [35].

More recently, the use of angiotensin converting enzyme (ACE) inhibitors has been implicated in the occurrence of hyperkalaemia [9]. In essence, ACE inhibitors reduce the concentration of angiotensin II and hence the production of aldosterone. The serum concentration of potassium may therefore increase, particularly when the efficiency of renal function is decreased. If the ACE inhibitor itself has caused renal failure, hyperkalaemia may become dangerous. ACE inhibitors may also cause hyperkalaemia when administered concurrently with other diuretics.

The treatment of hyperkalaemia in the preoperative period includes the use of resonium cation exchange resins, peritoneal dialysis, haemofiltration and haemodialysis [5]—for example, rectal or oral resonium if the serum concentration of potassium is increasing but has not exceeded 6.0 mmol litre^{-1}. The dose of calcium cation exchange resonium would be 15–30 g repeated 6-hourly if necessary. If the serum concentration of potassium has increased to more than 6.0 mmol litre^{-1}, constant ECG monitoring is mandatory and glucose 50 g and insulin 12 u should be given i.v. This therapy should continue until dialysis is provided. If overt arrhythmias occur during this period, 10 % calcium gluconate 10 ml (maximum dose 50 ml) and sodium bicarbonate may be given [D. J. Fisher, personal communication], although these agents must be administered through separate i.v. cannulae.

Renal transplantation offers the best long-term solution to the artificial control of the serum concentration of potassium. However, rapid decreases in serum concentration of potassium may reveal toxic symptoms related to other therapeutic agents, for example arrhythmias associated with cardiac glycosides.

ANAESTHESIA

Premedication

There is very little evidence available to indicate that any of the agents used commonly for premedication cause any acute changes in the serum concentration of potassium. However, recently it has been shown that preoperative anxiety causes a small decrease in serum potassium concentration [19]. It is possible that anxiety causes an increase in the concentration of endogenous catecholamines which, in turn, reduces the serum concentration of potassium, probably by stimulation of sodium–potassium ATPase. Suitable anxiolytic premedication would be expected to prevent such changes.

In an anxious patient, however, a combination of hypokalaemia, increased plasma concentration of adrenaline and administration of a volatile agent such as halothane might be expected to cause arrhythmias during induction of anaesthesia.

Induction of anaesthesia

Induction of anaesthesia in the presence of a low serum concentration of potassium rarely causes difficulties. The evidence suggests that, providing Pa_{CO_2} remains normal, some intracellular movement occurs. However, if the Pa_{CO_2} is greater than normal, the serum concentration of potassium increases slightly.

The most serious problems are caused by an acute increase in serum concentration of potassium. In normal patients, suxamethonium chloride 1 mg kg^{-1} i.v. causes the serum concentration of potassium to increase by a maximum of 1.0 mmol litre^{-1} [2]. There are several conditions, however, in which i.v. suxamethonium may cause sudden and very dangerous increases in the serum concentration of potassium, as a result of a massive outflow of intracellular potassium. Although the increase may not occur at the first exposure to suxamethonium, it may follow subsequent use. The major cause of this outflow seems to be cell membrane hypersensitivity [11], the exact duration of which is generally unknown. The main conditions [17] associated with i.v. suxamethonium and hyperkalaemia are as follows:

Burns. It has been recommended that suxamethonium is used on the first occasion but not thereafter [28]. Others have argued that suxamethonium-induced hyperkalaemia occurs only during the first 18–66 days after a burn [10]. However, this is by no means universally accepted.

Major trauma. A group of patients with major trauma were compared with another control group of normal patients [23]. The increase in serum concentration of potassium associated with suxamethonium in the first group was significant and dangerous, reaching, in some subjects, approximately 9.5 mmol litre^{-1}.

Tetanus. A significant increase associated with cardiovascular changes has been reported [17].

Muscle dystrophies. Observations similar to those in patients with tetanus have been recorded [34].

Paraplegia. The course is similar to that seen in burned patients. There is a short safe period, followed by a period of increased risk from about 14–28 days [32].

Cerebrovascular accidents. The course with these conditions is similar to that associated with burns patients and lasts at least 6 months [31, 37].

Uraemia. If the serum concentration of urea is increased in association with increased serum potassium, the use of suxamethonium is contraindicated [25]. There is no similar consensus when the concentration of urea is increased but that of potassium is normal.

Miscellaneous conditions. Congenital cerebral palsies, upper motor neurone disease and pseudo hypertrophic muscular dystrophies have all been associated with suxamethonium-related hyperkalaemia [35].

It would seem prudent to avoid the use of suxamethonium in all these conditions, but there may be circumstances in which suxamethonium would have considerable advantages—for example in a patient with a full stomach requiring emergency surgery. Here the anaesthetist is faced with a dilemma. If it is felt that advantages gained by the use of suxamethonium outweigh the disadvantages, what pharmacological strategies might the anaesthetist devise in order to prevent an increase in the serum concentration of potassium?

Some workers have advocated the use of a small pre-dose of a non-depolarizing neuromuscular blocker, but the efficacy of this manoeuvre has not been proven. One of the most interesting methods, proposed by James, Cork and Dennett [14], has been to pretreat patients with magnesium sulphate. Two groups of 10 patients received either i.v. saline or magnesium sulphate 60 mg kg^{-1}. The serum concentration of potassium was measured after administration of suxamethonium 1.5 mg kg^{-1} i.v. In control patients the serum concentration of potassium increased by an average of 0.57 (SD 0.2) mmol litre^{-1}, while in the magnesium sulphate group the increase was 0.05 (0.02) mmol litre^{-1} (a statistically significant difference).

How might magnesium sulphate exert such an effect, since the intubating conditions were the same in both groups? It is possible that magnesium sulphate itself causes muscle paralysis or prevents muscle from contracting (it is known that large concentrations antagonize the movement of calcium ions into the cell), and that magnesium prevents potassium efflux from the myocardial cells (as observed in isolated rat hearts).

The use of magnesium sulphate has not yet been fully investigated in patients known to be at risk from suxamethonium-induced hyperkalaemia, but has potential.

If an anaesthetist notices the classical sequential ECG changes associated with hyperkalaemia after i.v. suxamethonium, what therapeutic options are available? Either the effects of potassium on the myocardium may be antagonized, or the potassium may be redistributed into the cells [37]. Whichever method is used, immediate hyperventilation with increased concentrations of oxygen is also required because alkalosis encourages potassium ions to enter the cells.

Calcium chloride is the most commonly available treatment for acute hyperkalaemia. Slow i.v. injection of 10% calcium chloride 10–20 ml, using direct ECG control, usually restores myocardial excitability within 1–2 min. This effect may persist for up to 20 min.

The drug most easily available for the promotion of intracellular redistribution of potassium is sodium bicarbonate given i.v. at a dose of approximately 1 mmol kg^{-1}. The effect of a bolus dose is maximal at about 5 min, but then declines rapidly. It must be remembered, however, that calcium salts and bicarbonates should not be mixed together, as calcium bicarbonate is formed.

In the longer term, glucose with insulin is a preferred regimen but, in an average operating theatre, this combination may take around 10 min to prepare. Vitez [37] has recommended an immediate i.v. injection of 50% glucose 50 ml plus insulin 10 u. A maintenance solution of 10–25% glucose with insulin 1 u per 2 g of glucose is infused at 300–500 ml h^{-1} and sustained for at least 6 h.

Finally, there is evidence that β_2-adrenergic agents [36], particularly adrenaline, are effective in rapidly reducing the serum concentration of potassium. This technique is not used commonly in the United Kingdom.

Maintenance of anaesthesia

Factors which were important during the induction of anaesthesia continue to influence serum concentrations of potassium during anaesthesia. Once again, changes associated with hyperkalaemia are particularly important and dangerous in the maintenance phase.

Most dangerous is the development of malignant hypertonic hyperpyrexia [22]. This syndrome is triggered usually by exposure to fluorinated hydrocarbons, suxamethonium or a combination of both. Although the main thrust of treatment consists of i.v. dantrolene, oxygenation and cooling, the serum concentration of potassium does increase quickly and must be treated as discussed earlier.

Hypoxia and increased plasma concentrations of catecholamines also cause hyperkalaemia, probably as a result of decreased membrane stability and losses from hepatic cells [35].

Accidental or therapeutic hypothermia may cause hyperkalaemia. In addition, hypothermia renders the myocardium more sensitive to the action of an increased serum concentration of potassium [35].

Finally, some anaesthetists inject various substances relatively quickly. Some substances, such as penicillins, are potassium salts. It may therefore be prudent not only to inject a small amount as an initial test dose, but also to inject the remaining solution slowly.

The major factor that has, in the past, caused acute hypokalaemia has been an extracorporeal circulation [20]. This has been associated also with a metabolic acidosis and delayed insulin response [3]. However, many centres now utilize a cardioplegic solution to arrest the heart in diastole [22]; this solution contains large concentrations of potassium and generally prevents the occurrence of hypokalaemia traditionally associated with an extracorporeal circulation.

Acute or chronic hypokalaemia in the maintenance phase of anaesthesia may cause muscle weakness and intermittent positive pressure ventilation is recommended. If neuromuscular blocking drugs are used, it seems advisable that the loading doses of non-depolarizing agents should be reduced and neuromuscular transmission checked repeatedly with a nerve stimulator. Any subsequent doses should be smaller than normal and governed by the results obtained with the nerve stimulator. It would also seem reasonable that, if hypokalaemia is present, Pa_{CO_2} should be maintained within the normal range.

Postoperative period

Acute hyperkalaemia occurs very rarely in the postoperative period. However, it has been associated with renal failure, iatrogenic causes and after liver and renal transplantation [15].

Hypokalaemia is far more common. This may cause difficulties in reversing non-depolarizing neuromuscular block and, occasionally, cardiac irregularities and hypotension. It may be that a prolonged period of artificial ventilation may be required until the serum concentration of potassium is restored to the normal range, cardiac arrhythmias disappear and full muscle power returns.

It has been calculated that potassium loss is about 100 mmol day^{-1} for the first 2 days after surgery [26]. Thereafter, on average, the loss is 24 mmol day^{-1}, but this may increase following adrenal or bowel surgery. These losses should be replaced. The quantities of potassium required should be governed by the results of laboratory investigations, but does not normally exceed 15–20 mmol h^{-1} or approximately 500 mmol per 24 h.

LOCAL ANALGESIA

Generally, it would seem that the actions of local anaesthetic agents are unaffected by variations in serum concentration of potassium. However, in a small series of patients, continuous extradural analgesia has been associated with reduced loss of potassium in the postoperative period [4].

Some local anaesthetic preparations include potassium salts to potentiate their actions [1]. This combination has caused oedema in the area surrounding an injection site. Further, there is some evidence that, after infiltration of local anaesthetics for dental surgery, some changes occur in serum concentration of potassium [24].

There is no evidence as yet that continuous extradural infusion of opioids has any effect on potassium concentrations.

CONCLUSION

Potassium ions have an important role in the biology of man. Variations between intracellular and extracellular concentrations may affect many cellular functions. Acute changes in potassium concentrations may be very dangerous and occasionally lethal. The role of these ions in anaesthetic practice mirrors these statements.

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

EXETER MEETING

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All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

SPINALLY MEDIATED ANTINOCICEPTIVE EFFECTS OF XYLAZINE, AN ALPHA-2 ADRENOCEPTOR AGONIST: INTERACTION WITH SPINAL CORD OPIOID PATHWAYS

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Clinically useful analgesia following spinal administration of alpha-2 adrenoceptor agonists such as clonidine has been reported on several occasions [1]. The site of action responsible for this is assumed commonly to be in the spinal cord, as antinociceptive actions of such agents occur in animal models [2], but hypotension and nausea are common in man and segmental blocks have not been demonstrated. Animal studies have suggested that cross tolerance occurs between spinal adrenergic and opioid systems [3], but this conflicts with clinical use of clonidine in opioid-tolerant patients [1]. We have studied the interaction between the two systems in a preparation in which it was possible to show that drug action was at the spinal level.

Nociceptive thresholds (tail flick latency and electrical current) were measured in rats with implanted lumbar subarachnoid catheters. Segmental effects were demonstrated with electrical current in all tests. The adrenergic agonists used were clonidine and xylazine given intrathecally. First, the dose–response relationship for intrathecal xylazine (24.3–389 nmol) was investigated and a dose of xylazine equipotent with fentanyl 0.74 nmol in the electrical test was calculated.

The effects of naloxone and idazoxan (a selective alpha-2 adrenoceptor antagonist) on the antinociception caused by equipotent injections of fentanyl and xylazine were then investigated. Effects of both agonists given alone and with doses of idazoxan 6.7–540 nmol intrathecally and naloxone 2 mg kg^{-1} i.p. were measured. Antagonist effect was assessed as percentage suppression of control agonist response.

We were unable to demonstrate reliably segmental effects with clonidine. Xylazine caused increases in electrical thresholds in the tail, but not the neck, and a simultaneous increase in tail flick latency. Idazoxan caused a similar dose-dependent suppression of both these effects and the tail flick latency increase caused by fentanyl, but had no effect on fentanyl-induced increases in electrical current threshold. Naloxone suppressed totally all the fentanyl antinociception, but had no effect on xylazine.

We conclude that intrathecal xylazine produces antinociceptive effects by combining with spinal cord alpha-2 adrenoceptors; opioid propriospinal neurones are not involved. However, an alpha-2 adrenoceptor seems to be involved in some of the antinociceptive effects of intrathecal fentanyl.

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MALIGNANT HYPERTHERMIA: A GENERALIZED ABNORMALITY OF MEMBRANE FLUIDITY?

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Malignant hyperthermia (MH) is a rare but potentially serious complication of general anaesthetics. It has been suggested that the membrane defect responsible may be reflected in erythrocyte membranes. To test this hypothesis, erythrocytes were isolated from MH susceptible (MHS) and

TABLE I. *Calculated anisotropies for the membrane probes used in malignant hyperthermia susceptible (MHS) and non-susceptible (MHN) subjects*

Membrane probe	25 °C		37 °C	
	MHN	MHS	MHN	MHS
3-AS	0.101	0.109	0.101	0.098
6-AS	0.112	0.112	0.106	0.101
9-AS	0.099	0.100	0.099	0.094
12-AS	0.084	0.086	0.076	0.078
16-AP	0.075	0.076	0.064	0.066
DPH	0.246	0.243	0.192	0.186

non-susceptible (MHN) volunteers (as confirmed by muscle biopsy).

Membrane physical properties were estimated using a series of n-(9 anthroyloxy) fatty acids and diphenylhexatriene (DPH). Probes were incorporated into erythrocyte membranes and steady state anisotropy variables were quantified. A variety of anthroyloxy fatty acid probes were used, which reflect events at different depths in the membrane bilayer. DPH is believed to localize near the core and reflects the static component of membrane fluidity. Increasing anisotropy values reflect decreasing motional freedom of each probe. An increase in membrane fluidity with warming was apparent for all membrane probes used (table I).

There is therefore no difference in erythrocyte membrane physical characteristics between erythrocytes from MHS and MHN individuals.

IN VITRO CONTRACTURE WITH THE CALCIUM IONOPHORE A23187 IN SKELETAL MUSCLE FROM MALIGNANT HYPERTHERMIA SUSCEPTIBLE AND NORMAL INDIVIDUALS

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According to the European Malignant Hyperthermia Group [1], diagnosis of malignant hyperthermia susceptibility (MHS) depends upon abnormal *in vitro* contracture development with halothane and with caffeine, whilst an individual with an abnormal response to halothane alone or caffeine alone is designated as malignant hyperthermia equivocal (MHE).

The antibiotic A23187, which acts as a calcium ionophore, has been reported to produce a greater *in vitro* contracture in MHS muscle than normal muscle [2], and the addition of the A23187 contracture test was proposed as a means to reduce the number of equivocal diagnoses. In order to evaluate this proposal, we performed *in vitro* contracture studies with A23187 using muscle from MHS and MH negative (MHN) individuals. In all instances the muscle used for the study was surplus to diagnostic contracture study requirements.

Muscle specimens were taken from the vastus medialis muscle under regional anaesthesia and prepared for contracture testing according to the European MH Group protocol [1]. A baseline tension of 2 g was applied to the muscle fascicles, which were stimulated at 0.3 Hz throughout. A23187 was added for successive 3-min periods at 0.03125, 0.0625, 0.125, 0.25, 0.5 and 1 μmol litre^{-1}. The A23187 was prepared in dimethyl sulphoxide (DMSO) which, when tested separately at the concentrations used, had no effect on MHS or MHN muscle.

A23187 caused contractures in all muscle specimens tested. However, there was no basis, in terms of either threshold concentrations of ionophore required to produce a contracture or size of contracture produced, on which to differentiate between MHS and normal muscle.

We conclude that the A23187 contracture test has no role in the diagnosis of malignant hyperthermia.

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SERUM CONCENTRATIONS OF DANTROLENE FOLLOWING I.V. ADMINISTRATION

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Twenty-five patients (ASA I, aged 18–45 yr) presenting for day-case oral surgery on an afternoon list were given dantrolene 0.6 mg kg^{-1} i.v. as pretreatment before administration of suxamethonium during a study presented previously to the Society. Five minutes elapsed from the mid-time of administration to the induction of anaesthesia. Blood samples for measurement of serum concentrations of dantrolene were drawn from the arm opposite to that receiving drugs at 10, 15, 25 and, if possible, 45 min after dantrolene administration. Further blood samples were obtained at approximately 20 h after anaesthesia and, in most subjects, at 44 h at domiciliary follow-up visits.

All specimens were separated and frozen until required for assay. Serum dantrolene concentrations were assayed by extraction into hexanol–heptane and evaporation to dryness before passage through the HPLC system [1]. Coefficient of variation of the assay was 5% for dantrolene concentrations greater than 0.2 mg litre^{-1}.

No patient experienced any side effects attributable to dantrolene, in particular muscle weakness, nausea or vomiting. The mean age of the group was 27 yr (range 19–44 yr), weight 67 kg (range 46–83 kg) and sex distribution 10M:15F.

The mean concentration of dantrolene 10 min after administration was 1.43 mg litre^{-1} (range > 1–2 mg litre^{-1}). Mean concentrations decreased progressively to 1.03 mg litre^{-1} at 45 min, but there was still wide variation between individuals (table II).

Flewellyn and colleagues [2] found consistent blood concentrations when dantrolene was administered progressively to volunteers to achieve maximal muscle twitch depression, a total of 2.4 mg kg^{-1} (range 2.2–2.5 mg kg^{-1}) being given. One hour after administration, blood concentrations were 4.2 (SD 0.2) mg litre^{-1}, with an elimination half-life of 12 (SD 1.9) h. The mean concentration we observed at 45 min after 25% of this dose is consistent with their findings, but we cannot account for our wide variability. Our rate of elimination also shows a wide range, with 20-h concentrations varying in the range 0.01–0.61 mg litre^{-1} and a significant concen-

TABLE II. *Serum concentrations of dantrolene (mean* (SD) *[range]) after administration of 0.6 mg kg^{-1} i.v.*

Time	*n*	Concentration (mg litre^{-1})
10 min	24	1.43 (0.32) [0.94–2.07]
15 min	24	1.26 (0.33) [0.86–2.29]
25 min	25	1.14 (0.24) [0.68–1.57]
45 min	14	1.03 (0.32) [0.68–2.0]
20 h	25	0.25 (0.19) [0.01–0.61]
44 h	19	0.09 (0.09) [0.01–0.28]

tration of dantrolene in some patients at 44 h. Unlike Flewellyn's group, Meyler, Mols-Thurklow and Wesseling [3] found a very variable rate of elimination after a single oral dose of dantrolene, even allowing for erratic absorption. We feel that our sampling times, dictated by the main study, preclude further pharmacokinetic analysis of our data. However, dantrolene 0.6 mg kg^{-1} i.v. achieved blood concentrations in excess of 1 mg $litre^{-1}$.

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DESATURATION AND INDUCTION CHARACTERISTICS: COMPARISON OF PROPOFOL AND THIOPENTONE DURING MASK ANAESTHESIA WITH ISOFLURANE

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We studied 42 healthy patients presenting for minor urological, gynaecological and orthopaedic procedures. All gave informed consent to the trial which was approved by the Hospital Ethics Committee. Unpremedicated patients were allocated randomly to receive either propofol 2.5 mg kg^{-1} or thiopentone 4 mg kg^{-1}, a facemask was applied and they were allowed to breathe oxygen 3 litre min^{-1}, nitrous oxide 5 litre min^{-1} and 0.5% isoflurane from a Magill breathing system. The isoflurane was increased by 0.5% every 5 breaths until surgical anaesthesia was reached.

During each induction, a continuous record was made of Sp_{O_2} and inspiratory flow using an Ohmeda RGM5250 Monitor and chart recorder. Measurements of the following variables were obtained from the resulting tracings: preinduction Sp_{O_2}; minimum Sp_{O_2} during induction; time to regain preinduction Sp_{O_2}; initial apnoea; presence of breath-holding, cough, movement; percentage of induction period with an inspiratory flow > 12 litre min^{-1} (implying adequate ventilation); total time elapsed. Results were analysed by Student's *t* test and Fisher's Exact Probability test.

Mean preinduction Sp_{O_2} values were not significantly different between the two groups (table III), and mean minimum Sp_{O_2} was identical (86%). The patients who received propofol took longer to regain their initial Sp_{O_2} and, although this was not of statistical significance ($0.05 > P < 0.10$), the range of values was greater than that for thiopentone. The period of initial apnoea was significantly greater with propofol ($P < 0.05$). The mean time to surgical anaesthesia was virtually identical, but again the range of values was greater with propofol.

The incidence of coughing, breath-holding or movement was not significantly different between the groups.

A scoring system was used to quantify each induction, the following events each scoring one point: coughing; breath-holding; movement; initial apnoea > 40 s; Sp_{O_2} < 90% (+1 if < 80%); inspiratory flow > 12 litre min^{-1} for less than 75% of the total induction period (+1 if < 50%); total time > 365 s.

TABLE III. *Induction of anaesthesia with propofol or thiopentone (mean (SEM) [range])*

	Propofol ($n = 20$)	Thiopentone ($n = 21$)
Preinduction Sp_{O_2} (%)	96.7 (0.35)	95.8 (0.47)
Minimum Sp_{O_2} (%)	86.0 (1.70)	86.1 (1.40)
Time to regain preinduction Sp_{O_2} (s)	148 (23.5) [60–444]	105 (11.9) [36–192]
Initial apnoea (s)	55.6 (5.2)	38.5 (4.65)
Time to surgical anaesthesia (s)	363 (28.6) [182–734]	364 (19.9) [220–600]

A range of induction scores was obtained from 0 (smooth) to 9 (very stormy). The median score in each group was 3, and chi-square analysis showed no significant difference between the groups.

PRESSURE–VOLUME HYSTERESIS OF THE LUNGS IN RESPIRATORY DISTRESS SYNDROME

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High frequency ventilation (HFV) and extracorporeal removal of carbon dioxide ($ECCO_2R$) are new forms of respiratory support which are still being developed. Partial or complete lung apnoea is common in both. In this study we have examined the effects on lung volume and oxygenation of a sustained inflation in acutely sick lungs during apnoea. Carbon dioxide was removed by an extracorporeal lung.

Six adult rabbits were anaesthetized, placed in a whole body plethysmograph and connected to an extracorporeal lung via venous cannulae. Respiratory failure was induced by repeated saline lavage (20 ml kg^{-1} × 3–6) to the lungs, until the arterial oxygen tension (Pa_{O_2}) decreased to less than 50 kPa with $FI_{O_2} = 1$. Pressure–volume hysteresis of the lungs was measured before and after lavage.

Baseline (before sustained inflation) expired lung volume (ELV) and Pa_{O_2} values were recorded after 2 min at constant airway pressure of 0.65 kPa. A sustained inflation was performed by increasing the airway pressure from 0 to 3.5 kPa for 10 s. The airway pressure was then allowed to return to 0.65 kPa and maintained for a study time of 5, 10, 20, 30 or 40 min, chosen randomly. At these times, Pa_{O_2} and ELV were measured.

Pa_{O_2} and ELV were substantially greater following a sustained inflation and maintained for 40 min (table IV). Pressure–volume hysteresis was greater following lavage, as shown in a previous study [1].

These results suggest that sustained inflation allows recruitment of lung volume and improvement in oxygenation by exploiting pressure–volume hysteresis. The recruited lung volume can then be maintained by apnoea for at least 40 min. Thus those methods of ventilation which avoid large tidal volumes such as HFV [2] and $ECCO_2R$ [1] may, in the acutely sick lung, allow good arterial oxygenation to be

TABLE IV. *Expired lung volume (ELV) and arterial oxygen tension* (Pa_{O_2}) *as functions of time (mean* (SEM)). *$^*P < 0.05$ compared with 10 and 20 min; $^{***}P < 0.001$ compared with all times*

Time (min)	ELV (ml)	Pa_{O_2} (kPa)
0	7.0 (0.6)***	14.6 (2.1)*
5	17.5 (3.2)	24.3 (6.0)
10	15.5 (1.9)	31.1 (7.7)
20	15.9 (2.3)	28.5 (7.1)
30	16.5 (2.1)	26.8 (7.5)
40	14.7 (1.7)	23.9 (6.3)

achieved at a smaller airway pressure by the use of a sustained inflation.

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A RAPID METHOD TO ASSESS CHEST WALL SHAPE AND VOLUME CHANGE

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Chest wall movement is often described in terms of ribcage and abdominal volume contributions. If each compartment moves in a congruent manner, a single dimension of each (a diameter or a cross-section) may describe the motion of the whole. When tidal volume and a dimension of each compartment are measured simultaneously, an algebraic method such as linear regression [1] gives a relationship between the chosen dimension and the volume change of the compartment.

Because anaesthesia can alter the co-ordination and position of the chest wall, these assumptions may fail, and a more exact and detailed measure of motion may prove to be useful. We describe an optical method for chest wall measurement. A low energy HeNe laser beam generates a plane of light that can be moved rapidly (1 ms), by means of a galvanometer-mounted mirror, to fall at different positions across the chest wall. A video camera is placed so that the image of the resultant line falls across the raster scan, and the line shape is derived by electronic processing of the video signal in the blanking period between successive image scans. Subsequent digital analysis allows data to be presented within 3 min of measuring a 108-s episode of movement.

Direct measurement of simple ideal and complex shapes gives reproducible results (SD 4 ml). To measure ventilation, the data from five line positions may be used indirectly, as in previous methods, by regression against a spirometer signal, or volume change of the visible surface may be calculated directly.

This preliminary study was of seven healthy supine male subjects unaccustomed to ventilatory measurements. Breathing was measured by wedge spirometry and compared with volume estimates from chest and abdominal signals from inductance bands and magnetometers and the optical system used both directly and indirectly. With regression methods, the SD of the difference (wedge − estimate) was poorer for magnetometer signals than for the optical method (57 *vs* 31 ml, $P < 0.05$, Wilcoxon) but identical for inductance and optical methods (40 ml in both cases). These findings confirm the validity of the original assumptions of Konno and Mead [2] for quiet breathing in conscious subjects. Direct calculations of volume change gave a systematic underestimate of volume between 0 and 34%, probably because some motion at the edges of the chest wall is not seen.

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LEFT VENTRICULAR FUNCTION DURING TRANSOESOPHAGEAL ECHOCARDIOGRAPHIC ASSESSMENT OF ABDOMINAL AORTIC ANEURYSM RESECTION

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Aortic clamping and release may be associated with significant haemodynamic changes [1]. Transoesophageal echocardiography (TOE) provides a method of measuring ejection fraction and estimating left ventricular preload during operation [2].

Following Ethics Committee approval, we studied 10 patients undergoing infrarenal aortic aneurysm resection. Ejection fraction was assessed before operation using radionuclide angiocardiography. Radial and pulmonary artery catheters were inserted before induction of anaesthesia. Standardized anaesthesia consisted of thiopentone 3–5 mg kg^{-1}, vecuronium 0.1 mg kg^{-1} and fentanyl 5–8 µg kg^{-1}, ventilation to normocapnia with nitrous oxide and 0.25–1% isoflurane in oxygen. A 5-MHz TOE probe (Hewlett-Packard 77020) was positioned to view the short axis of the left ventricle. Haemodynamic data, including heart rate, arterial pressure, pulmonary artery occlusion pressure (PAOP), thermodilution cardiac output and systemic vascular resistance (SVR), were collected 5 min before and after both clamping and release. TOE data consisting of left ventricular cross sectional areas at end diastole (EDA) and end systole (ESA) were recorded on videotape and analysed later. Area ejection fraction (AEF) was calculated as:

$$AEF = (EDA - ESA)/EDA$$

AEF measured before operation (51.9 (SD 13.8)%) did not

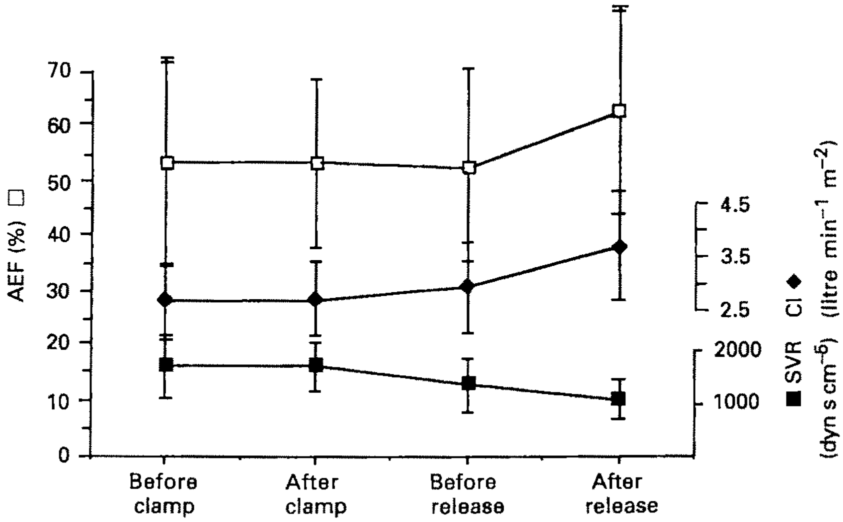

FIG. 1. Changes in area ejection fraction (AEF), cardiac index (CI) and systemic vascular resistance (SVR) in relation to aortic clamping and release.

differ from that measured before (53.5 (19.4)%) or after (53.3 (15.6)%) application of the clamp. A trend of increasing AEF at clamp release was evident (52.7 (17.6)% before; 62.3 (18.4)% after) and this was associated with a significant increase in cardiac index (from 3.0 (0.8) litre min^{-1} m^{-2} to 3.8 (1.0) litre min^{-1} m^{-2} ($P < 0.05$)) and a significant reduction in SVR (from 1270 (491) dyn s cm^{-5} to 999 (317) dyn s cm^{-5} ($P < 0.01$)) (fig. 1). Preload, as assessed by both PAOP and EDA, was unchanged. There was no significant correlation between EDA and PAOP in any patient.

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AGE-DEPENDENT VARIATION IN RESPONSE TO TUBOCURARINE IN THE ISOLATED RAT DIAPHRAGM

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Although there is clinical evidence that human neonates are sensitive to the effects of non-depolarizing neuromuscular blocking drugs [1], evidence from animal experiments is scarce. We have studied the dose–response relationship for tubocurarine in phrenic nerve–hemidiaphragm preparations from rats aged 0–46 days.

Sprague–Dawley rats aged from a few hours to 46 days were killed with ether. The left hemidiaphragm and phrenic nerve were removed and mounted in a 100-ml organ bath containing modified Kreb's solution maintained at 37 °C, pH 7.4 and aerated with 95% oxygen and 5% carbon dioxide. The nerve was stimulated supramaximally at 2 Hz for 2 s every 10 s via a suction electrode, and the resulting twitch tension of the muscle was measured and recorded.

After 20 min for stabilization, increments of tubocurarine 5×10^{-5} mol litre^{-1} were added to the bath to provide a range of concentrations between 5×10^{-8} and 10^{-4} mol litre^{-1}. Maximum depression of twitch height and the train-of-four (TOF) ratio were recorded after a further 15–30 min. Individual dose–response curves were constructed, from which the dose required to produce 50% depression of twitch (EC_{50}) was estimated.

The diaphragm of the newborn rat is not unduly sensitive to tubocurarine compared with that of the adult, but sensitivity develops during the first week of extrauterine life (fig. 2). This period is characterized also by complete absence of

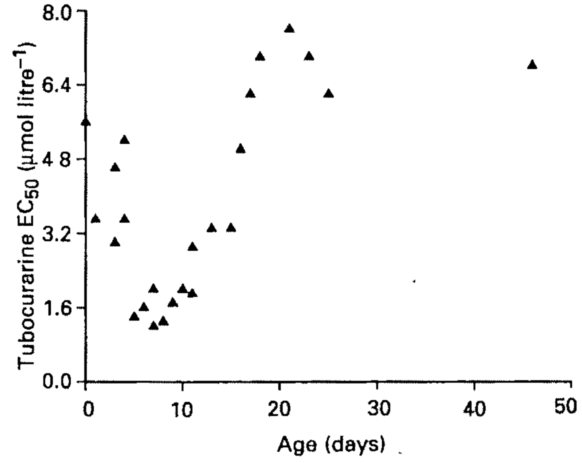

FIG. 2. Age-related dose of tubocurarine required to produce 50% depression of twitch (EC_{50}).

TOF fade. Sensitivity to tubocurarine decreases and TOF fade appears over the next 10–14 days; by 21 days the adult EC$_{50}$ and pattern of TOF fade are established. These results may be explained in part by the change-over from fetal to adult type acetylcholine receptor channels which takes place at 0–21 days in the rat [2]. The loss of sensitivity to tubocurarine and the appearance of TOF fade from 8 days may indicate increased transmitter release and the development of a positive feedback mechanism for acetylcholine. The response of the 10–11 day old rat to tubocurarine is similar to that of the human neonate [1].

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POTENTIATION AND ANTAGONISM OF VECURONIUM BY DECAMETHONIUM IN MAN

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Krieg, Hendrickx and Crul [1] demonstrated that vecuronium showed a 60% reduction in ED$_{95}$ when administered after suxamethonium 1.5 mg kg^{-1} (ED$_{95}$ 19 0 µg kg^{-1} compared with 31.6 µg kg^{-1} when given alone). In the present study we have administered decamethonium before or after vecuronium to determine if there was any additive or synergistic effect.

Five adult patients (ASA I or II) were studied in each of two groups, matched for age and weight. The anaesthetic consisted of thiopentone 4–6 mg kg^{-1} followed by 67% nitrous oxide and 1.0% isoflurane in oxygen. A Datex Relaxograph was set up to record neuromuscular conduction in the hypothenar muscles of one hand and a period of stabilization was allowed. The first group received decamethonium 0 1 mg kg^{-1}. Following recovery of T1 to $\geqslant 90\%$ of its initial value for $\geqslant 80$ s, a cumulative dose–response curve to vecuronium was obtained, using an initial dose of 3 µg kg^{-1}, with 3-µg kg^{-1} increments up to a total of 12 µg kg^{-1} (a range established in an initial study of two patients). In the second group, a cumulative dose–response curve to vecuronium was obtained using an initial dose of 20 µg kg^{-1}, with 10-µg kg^{-1} increments up to a total of 40 µg kg^{-1}. Following spontaneous recovery of T1 to 25–30% of its initial value, decamethonium 0.1 mg kg^{-1} was administered and the effect on T1 and T4 recorded.

The ED$_{50}$ for vecuronium alone was 30 µg kg^{-1} and that after recovery from decamethonium block was 4 µg kg^{-1}—an approximately seven-fold potentiation of the effect of vecuronium. The two log dose–response curves were parallel. Administration of the same dose of decamethonium during recovery from vecuronium neuromuscular block antagonized the block; this effect was initially greater on T4 than T1, but was followed by a secondary decrease in T4, whilst the recovery of T1 was maintained.

Depolarizing drugs produce an agonist block at the postsynaptic membrane [2]. Competition between the agonist drug, decamethonium, and the antagonist block of vecuronium at this site could explain the observed antagonism of vecuronium. Although Krieg, Hendrickx and Crul [1] suggested that the potentiation of vecuronium seen after suxamethonium was a pharmacokinetic effect resulting from reduced metabolism of vecuronium after suxamethonium, there is no evidence for such an effect, or evidence to explain the antagonism of vecuronium block by decamethonium on this basis. We propose that the cause of the marked potentiation of vecuronium found after decamethonium and suxamethonium is the result of a presynaptic blocking effect produced by these agents [3], which in turn is responsible for the Phase II effects observed after prolonged administration.

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POTENCY AND EASE OF ANTAGONISM OF PIPECURONIUM IN CHILDREN

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Pipecuronium is a long-acting, non-depolarizing steroid neuromuscular blocking drug. It is about 20% more potent than pancuronium, with a similar duration of action but fewer cardiovascular side effects [1]. We have studied the potency, clinical duration of action and ease of antagonism of pipecuronium in neonates, infants and children.

The study was approved by the Ethics Committee of the Frankfurt University Hospital. For each child, written informed consent for participation was obtained from the parents. We studied 25 normal children (ASA I) during elective surgery under nitrous oxide and 1.5 vol% halothane (maximal inspiratory concentration) in oxygen anaesthesia. There were five groups of five children: 1–12 months, 13–24 months, 25–36 months, 37–72 months, and children older than 72 months.

The action of pipecuronium was measured mechanographically by a method published previously (supramaximal ulnar nerve stimulation, train-of-four (TOF), age-adjusted preload [2]) After inhalation induction of anaesthesia, the children received cumulative doses of pipecuronium until 95% suppression of the first stimulus response (T1) for determination of the individual ED$_{95}$. The time from the last injection to recovery of T1 to 25% of the initial value was measured as the clinical duration of action (D$_{25}$) At the end of D$_{25}$, residual block was antagonized with neostigmine 0.03 mg kg^{-1}. For assessment of recovery, times from administration of neostigmine to recovery of T1 to 90% (N-T1$_{90}$) and to recovery of the TOF ratio to 0 7 (N-TOF$_{0 7}$) were recorded. Results are presented in table V.

The ED$_{95}$ in the neonates studied was only 50% that observed in the older children; this difference was significant. In the neonates, the clinical duration of action of ED$_{95}$ was significantly shorter. In all age groups, the residual neuromuscular block at termination of the clinical duration of

TABLE V. *Results (mean (range))*

Age (months)	ED_{95} (mg kg^{-1})	D_{25} (min)	N-T1_{90} (min)	N-TOF$_{0.7}$ (min)
1–12	0.025 (0.015–0.04)	12.5 (6–18)	3.5 (2.5–5.5)	4 (2.5–5)
13–24	0.044 (0.04–0.05)	17 (12–21.5)	4 (3–6)	5.5 (3 5–7.5)
25–36	0.05 (0.05–0.055)	15 (10–20)	5 (5–5.5)	5.5 (5.5–6)
37–72	0.047 (0.035–0.055)	15.5 (11.5–19)	4.5 (3–6)	4.5 (3.5–5.5)
> 72	0.049 (0.03–0.055)	21 5 (12–31)	5 (3–7)	5 (4.5–7)

action could be antagonized within a few minutes by administration of neostigmine 0.03 mg kg^{-1}.

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RESPONSE TIME OF FINGER AND EAR PULSE OXIMETER PROBES DURING HYPOXAEMIC EVENTS OCCURRING DURING ANAESTHESIA

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Pulse oximeters are assumed to provide a measurement of oxygen saturation throughout the body. This generalization may be true in the steady state, but under dynamic conditions oximetry only gives an accurate assessment of saturation at the actual point of measurement. Severinghaus and Naifeh [1] induced hypoxaemia in normal subjects and found response delays of up to 50 s and 10 s for saturation readings obtained from pulse oximeter probes placed on finger and earlobe, respectively. The purpose of this study was to determine if similar delays between finger and ear probe responses were detectable during hypoxaemic events occurring during anaesthesia.

We developed a system comprising two Ohmeda Biox 3700 pulse oximeters, one with a finger probe and one with an ear probe, linked to a BBC B computer. A program was written which detected and recorded all events when the patient's oxygen saturation decreased to less than 93%. By using a constantly updated memory loop within the program, it was possible to start recording 1 min before the decrease and stop 1 min after saturation returned to normal.

After local Ethics Committee approval was obtained, the apparatus was used by all members of the department over a period of 6 months, during which time 28 hypoxaemic events were recorded.

Statistical analysis was by paired *t* and signed rank tests.

The mean minimum saturations recorded for ear and finger probes were 86.3% and 83 5%, respectively ($P < 0.01$). The overall mean delay for finger compared with ear probes was 4.4 s ($P < 0\ 01$). Analysis of the recordings at different saturations showed finger probe responses to be significantly slower than those of the ear probe at saturations equal to and greater than 91% ($P < 0.05$), but probe response times were not significantly different at lesser saturations (fig. 3).

We conclude that in these patients the use of finger probes would have given adequate warning of the onset of hypoxaemia. This may not be true in patients with poor peripheral perfusion.

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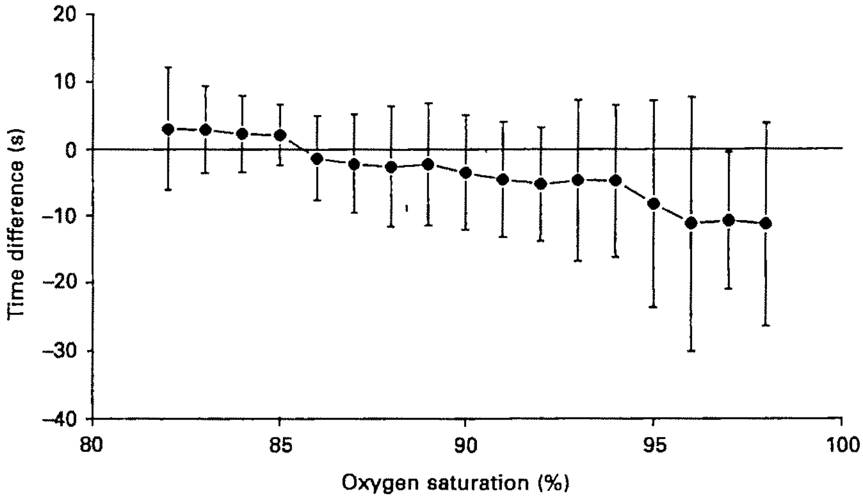

FIG. 3. Difference in response times (mean, SD) between ear and finger oximeter probes at different saturation values.

COMPUTERIZED ANALYSIS OF CONTINUOUS PULSE OXIMETRY IN CHILDREN WITH NOCTURNAL BREATHING DISORDERS

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Pulse oximetry is a recognized investigation in the determination of the severity of Obstructive Sleep Apnoea (OSA), the commonest form of nocturnal breathing disorder [1]. Night time hypoxaemia has been shown to occur in 34% of children presenting for elective adenotonsillectomy [2]. The aim of this study was to investigate if a clinical history of nocturnal breathing disorder carried a greater risk of developing nocturnal hypoxaemia.

Fifteen children (2–9 yr) with a history of nocturnal breathing disorder and awaiting ENT surgery, were studied overnight with a system of computerized pulse oximetry described previously [3].

Data were analysed in three ways:

(1) Hypoxic episodes (arterial oxygen saturation (Sp_{O_2}) less than 85% for > 20 s); number, duration and time of occurrence.

(2) Sp_{O_2} distribution throughout the study, expressed as percentage time spent at a given Sp_{O_2}.

(3) Compressed spectral array: hourly Sp_{O_2} distribution as a spectrum of Sp_{O_2} values against time. These can have either "stable" or "unstable" patterns (an unstable pattern is defined as a variation between the hourly peaks of $Sp_{O_2} > 4\%$).

The first 1 h of monitoring provided a baseline Sp_{O_2} pattern and mean value in the awake child.

Eleven children had normal and four children had abnormal results, as shown by the number of hypoxic episodes and the percentage time of the Sp_{O_2} distribution > 94% (table VI). Baseline mean Sp_{O_2} during the awake 1 h of monitoring demonstrated no difference between the two groups. The compressed spectral arrays for each child had a stable pattern for the normal group (children Nos 1–11), and an unstable pattern for the abnormal group (children Nos 12–15).

These results suggest that a history of a nocturnal breathing disorder *alone* is a poor indicator of significant periods of nocturnal hypoxaemia.

TABLE VI. *Age and results of oximetry analysis in 15 children with nocturnal breathing disorders (individual results, mean (range))*

	Patient No.				
	1–11	12	13	14	15
Age (yr)	4.75 (2–9)	6	3.5	7	3.5
Number of hypoxic episodes	1.36 (0–4)	22	66	17	38
Percentage time with $Sp_{O_2} > 94\%$	(95.4–99.9)	93.3	55.4	91.2	89.1
Baseline Sp_{O_2}: hourly mean value (%)	(95.5–99.6)	97.9	96	96.4	97.9

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PREOXYGENATION: USE OF A HIGH FLOW DELIVERY SYSTEM

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There is little agreement on which techniques are optimal for preoxygenation [1]. Most of the techniques described involve use of a semi-open breathing system with a tight gas seal of the patient–mask interface. Many patients find this unpleasant. This study investigated the use of an alternative, high inflow semi-open system.

Seventeen trained volunteers (10 male) were recruited into the study. The semi-open system comprised a disposable Hudson facemask attached via plastic tubing to the common gas outlet of an anaesthetic machine. The oxygen rotameter was set at 8 litre min^{-1} and the oxygen flush device was held open continuously, achieving a total flow rate of 48 litre min^{-1}. The end-point for preoxygenation was the time for the peak expired nitrogen concentration to decrease to less than 5%. Nitrogen concentration was measured using a mass spectrometer (Centronics MGA), sampling from a fine-bore catheter positioned in the nasopharynx. Before preoxygenation, the average peak inspiratory flow rate of each volunteer was determined using a Fleisch pneumotachograph. Each volunteer also underwent preoxygenation using the Mapleson A system, with an oxygen flow rate of 100 ml kg^{-1} min^{-1}.

Preoxygenation was achieved at mean 138 (SD 31.3) s and 159 (41.6) s with the semi-open and Mapleson A systems, respectively ($P < 0.05$, paired t test; 95% confidence interval for the difference, 14.7–37.3 s). One of the volunteers did not satisfy the criteria for preoxygenation with the semi-open system because his peak expired nitrogen did not decrease to less than 10%; his peak inspiratory flow rate before preoxygenation was 70 litre min^{-1}.

The results suggest that this system provides a favourable alternative for preoxygenation, provided that peak inspiratory flow rate is not excessive.

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INFLUENCE OF THERAPEUTIC SUGGESTIONS DURING GENERAL ANAESTHESIA ON RECOVERY IN PATIENTS UNDERGOING HYSTERECTOMY

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It has been suggested that positive therapeutic suggestions presented during anaesthesia may lead to significantly better quality of recovery and shorter duration of hospital stay after abdominal hysterectomy [1]. However, initial demonstrations of a similar phenomenon after cholecystectomy could not be substantiated [2,3]. Thus it is not entirely clear that any improved recovery is related directly to intraoperative suggestions. The aims of this study were to investigate if the significant improvement in recovery variables after hysterectomy was reproducible, and if improvement could be related to the continuous presence of a reassuring voice, rather than the content of the message.

This was a double-blind, randomized study which involved 75 patients (ASA Grade I or II) undergoing total abdominal hysterectomy. Written informed consent was obtained from all patients. They were allocated randomly to one of three groups to whom different tapes were played during surgery: therapeutic suggestions which were identical to those used in a previous study [1]; a neutral message; a blank tape with no message. The same speaker was used on the tapes which contained a message. Tapes were coded and the double-blind nature of the study was maintained carefully throughout.

All patients were premedicated with papaveretum 0.15 mg kg^{-1} and prochlorperazine 0.18 mg kg^{-1}, and received a standard general anaesthetic comprising thiopentone 5 mg kg^{-1}, vecuronium 0.1 mg kg^{-1} and papaveretum 0.1 mg kg^{-1}. The patient's lungs were ventilated with 67 % nitrous oxide and 0.75–1.25 % enflurane in oxygen. The tapes were played continuously throughout the operation. The patients were followed up daily after the operation. The following were assessed and recorded: pain score; analgesic requirement; anxiety and mood states; complications such as nausea, flatulence, pyrexia, infections; ease of mobility; duration of hospital stay.

None of the patients reported conscious recall of the messages or other intraoperative events. In contrast to the original study [1], there were no significant differences in the recovery variables studied. In addition, there were no differences in nursing assessment of the quality of recovery of patients in the three groups. In conclusion, no improved recovery related either to the presence of a voice or the content of the message was demonstable in this study.

ACKNOWLEDGEMENT

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FEMORAL ARTERIOVENOUS EXTRACORPOREAL REMOVAL OF CARBON DIOXIDE USING A HOLLOW FIBRE MEMBRANE LUNG

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Extracorporeal removal of carbon dioxide ($ECCO_2R$) is a form of respiratory support which permits reduction or cessation of pulmonary ventilation, and consequently offers the potential to reduce barotrauma in respiratory distress syndromes. The purpose of the present study was to examine the feasibility of using a haemofiltration vascular access, pumping and monitoring system coupled to a membrane lung to achieve high rates of elimination of carbon dioxide from low extracorporeal blood flows.

TABLE VII. *Percentage of the total carbon dioxide elimination (CO_2 elim.) achieved with the membrane lung (mean (SD)). $\dot{Q}b$ = Membrane lung blood flow*

	Spontaneous flow	Pumped flow
Normocapnia		
Pa_{CO_2} (kPa)	5.09 (0.40)	5.39 (0.65)
$\dot{Q}b$ (ml min^{-1})	208 (84)	605 (7.0)
CO_2 elim. (%)	34 (12)	71 (8)
Hypercapnia		
Pa_{CO_2} (kPa)	7.49 (0.63)	7.30 (0.50)
$\dot{Q}b$ (ml min^{-1})	206 (73)	477 (119)
CO_2 elim. (%)	53 (17)	86 (11)

Six sheep (37–84 kg) were anaesthetized with pentobarbitone and fentanyl and the lungs ventilated with oxygen using a pressure-limited ventilator (peak 20 cm H_2O, PEEP 3 cm H_2O) at a rate necessary to achieve either arterial normocapnia (Pa_{CO_2} 4.5–6 kPa) or hypercapnia (Pa_{CO_2} 6.5–8.5 kPa) with a minimum rate of 1 b.p.m. Arteriovenous extracorporeal blood flow was established via 10-French gauge femoral vessel catheters through a hollow fibre membrane lung (Capiox 350 5 m^2). Blood flow through the circuit was either spontaneous or pumped at 600 ml min^{-1} using a Gambro AK-10 pump/monitor system. Activated clotting time (Hemochron) was maintained at 200–300 s with heparin. Carbon dioxide elimination from the membrane lung and from the ventilator were measured by measuring mean expired gas flows and carbon dioxide concentrations.

Results are displayed in table VII.

The mean P_{CO_2} of the blood leaving the membrane lung was 0.61 (SD 0.32) kPa. The average carbon dioxide production of all the sheep was 178 (39) ml min^{-1}. In the pumped hypercapnia group, membrane lung elimination of carbon dioxide was so efficient that, even at 1 b.p.m., hypercarbia could not be maintained in some animals unless membrane lung blood flow ($\dot{Q}b$) was reduced.

We conclude that a carbon dioxide elimination equivalent to at least 70–80 % of resting adult human production of carbon dioxide may be achieved using a modest blood flow through a high efficiency membrane lung. The vascular access catheters used were standard human percutaneous types and the blood flow was controlled and monitored using a standard haemodialysis/filtration system.

THE ANTI-OXIDANT POTENTIAL OF PROPOFOL

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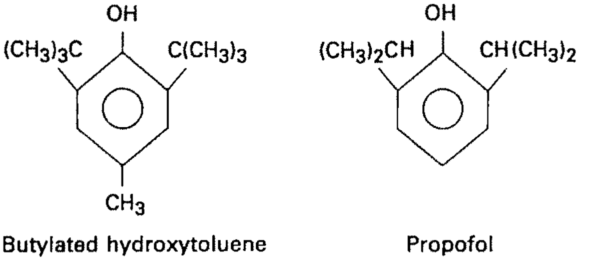
Free radical-mediated tissue injury may contribute to many disease processes. Conditions of particular relevance to the



Butylated hydroxytoluene Propofol

FIG. 4. Chemical structures of butylated hydroxytoluene and propofol.

anaesthetist include reperfusion injury, acute lung injury, severe sepsis and multi-system organ failure. Although the clinical value of boosting anti-oxidant defences is unclear, such therapies attenuate tissue damage in experimental models of radical-mediated organ injury.

Propofol has been shown to attenuate the cortical damage associated with a feline model of cerebral reperfusion injury [1]. Although the mechanism of this protection has not been defined, the chemical similarities between propofol and the well known food anti-oxidant, butylated hydroxytoluene (fig. 4), suggest that propofol also may be a free radical scavenger.

We have examined the anti-oxidant activity of propofol in an *in vitro* system developed to measure the total radical anti-oxidant potential (TRAP) of plasma [2]. In this system, the anti-oxidant capacity of propofol is equal to that of trolox, a water soluble analogue of vitamin E and known anti-oxidant. In contrast, 10% Intralipid, the vehicle for propofol in its clinical formulation, has no anti-oxidant activity. The addition of propofol to plasma at concentration of 20 μg ml^{-1} increased the plasma TRAP value from 967 (SD 62) μmol $litre^{-1}$ to 1172 (49) μmol $litre^{-1}$ ($n = 6$, 95% confidence interval of the difference = 132–277; $P < 0.0001$).

We conclude that propofol behaves as a peroxyl radical, chain breaking anti-oxidant—an effect that may be significant at clinically relevant concentrations.

ACKNOWLEDGEMENTS

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EFFECT OF INHALED SALBUTAMOL ON RESTING OXYGEN CONSUMPTION

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The effect of salbutamol on oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) has not been studied, but other catecholamines are known to increase basal metabolic rate [1].

Indirect calorimetry with an open canopy technique [2] was used to study 10 normal, non-smoking subjects (aged 20–46 yr, 42–94 kg, seven male) relaxing comfortably on a couch. All subjects were fasted and abstained from caffeine for 6 h before undergoing eight double-blind, cross-over studies on separate days. The study began with a rest period of 20 min followed by taking 2, 4, 8 or 12 puffs from unmarked inhalers containing either salbutamol (100 μg per puff) or placebo taken through a spacer. $\dot{V}O_2$ and $\dot{V}CO_2$ were measured continuously from 5 min before inhalation until 1 h thereafter. Measurements after inhalations were compared with the baseline values at the end of the rest period and expressed as percentage change. ECG and arterial pressure were monitored throughout.

The changes in $\dot{V}O_2$ and $\dot{V}CO_2$ 15 min after inhalation of salbutamol and placebo are shown in table VIII. At 60 min after inhalation, $\dot{V}O_2$ and $\dot{V}CO_2$ were still increased by 14.0 (4.3)% ($P < 0.01$) and 7.2 (1.7)%, respectively, with 8 puffs, and by 16.9 (3.6)% ($P < 0.05$) and 10.8 (4.0)%, respectively with 12 puffs.

In conclusion, inhaled salbutamol increased $\dot{V}O_2$ and $\dot{V}CO_2$ in the normal subject at doses greater than 400 μg. The larger doses administered by nebulizer are likely to cause marked increases in oxygen consumption.

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TABLE VIII. *Mean (SEM) percentage changes in* $\dot{V}O_2$ *and* $\dot{V}CO_2$ *15 min after inhalation of salbutamol or placebo compared with pre-inhalation baseline values in 10 subjects*: $^*P < 0.05$; $^{**}P < 0.01$

	Number of puffs			
	2	4	8	12
Salbutamol				
$\dot{V}O_2$	7.9 (2.8)	11.2 (2.6)**	19.5 (3.6)**	21.2 (3.4)**
$\dot{V}CO_2$	2.1 (2.9)	4.3 (2.4)	16.7 (2.7)*	19.9 (3.4)**
Placebo				
$\dot{V}O_2$	0.3 (3.2)	3.2 (1.2)	2.2 (1.6)	5.4 (2.5)
$\dot{V}CO_2$	−2.2 (4.2)	3.7 (1.6)	3.6 (2.9)	4.3 (2.5)

INVESTIGATION OF FADE IN SUXAMETHONIUM-INDUCED PHASE II BLOCK IN THE ISOLATED RAT DIAPHRAGM

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Fade at fast rates of stimulation has been described as characteristic of Phase II block. We studied the development of Phase II block, the onset of fade and its pharmacological characteristics.

Phrenic nerve–diaphragm preparations from Sprague–Dawley rats of both sexes were stimulated supramaximally at 0.1 Hz and 2 Hz. We performed three groups of experiments: (1) Using paired hemidiaphragms (from individual rats), we compared the effects of low-dose and of high-dose suxamethonium. (2) We studied the effects of neostigmine and 4-aminopyridine on twitch height (at 0.1 Hz) and fade (at 2 Hz) in early (Phase I) and late (Phase II) suxamethonium block, and compared them with the effects of the same drugs on a partial tubocurarine curare block. (3) We studied the effects of a subparalytic dose of tubocurarine on suxamethonium block.

(1) In experiments on the effect of dose of suxamethonium, the time course of Phase I and Phase II block was similar to that reported previously [1], although the initial increase in twitch height that has been reported was not seen. The onset of fade occurred after a variable period of exposure in different pairs of hemidiaphragms, but simultaneously in each of a given pair (i.e. independent of the dose of suxamethonium), and the amount of fade was similar in each of a given pair of diaphragms (i.e. also independent of the dose of suxamethonium).

(2) Neostigmine potentiated twitch depression and fade in early and late suxamethonium block. The same dose of neostigmine antagonized twitch depression and fade of a partial tubocurarine block. 4-Aminopyridine antagonized twitch depression, but not fade, of a partial early and late suxamethonium block. This effect was similar to (although slower than) that of a partial tubocurarine block.

(3) Pretreatment with tubocurarine 0.08–0.1 mg ml^{-1} (a dose which produced no depression of twitch height), potentiated the effect of a subsequent dose of suxamethonium. Fade was present from the onset of suxamethonium block and there was no clear distinction between Phase I and Phase II block.

Although fade is a feature of late (Phase II) suxamethonium block, in our experiments it appeared in both phases of the block. A similar observation has been made by Galindo [1] in the isolated rat diaphragm. 4-Aminopyridine fails to antagonize, or may even potentiate, fade in the presence of tubocurarine [2]. We found a similar effect on the fade of suxamethonium block. This observation, and the potentiation of suxamethonium-induced fade by tubocurarine, suggest that the two drugs may act through a similar presynaptic mechanism. Neostigmine-induced increase in acetylcholine concentration potentiates the presynaptic effect of an agonist drug. We therefore propose that fade and Phase II block of suxamethonium are presynaptic effects.

(Home Office Licence No. PIL 70/09433)

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COMPARISON OF BOLUS OR SLOW INFUSION OF PROPOFOL FOR INDUCTION OF ANAESTHESIA IN THE ELDERLY

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We have shown previously that slower rates of administration of propofol for induction of anaesthesia in elderly patients minimize the reduction in arterial pressure and the doses used [1].

After obtaining Ethics Committee approval and written informed consent, we studied 50 elderly patients (mean age 71 (range 60–82) yr, ASA I–II), undergoing elective surgery. Thirty patients were allocated randomly to receive propofol 600, 300 or 150 ml h^{-1} for induction of anaesthesia. Loss of verbal contact was taken as the end-point. In all groups, premedication was with temazepam 20 mg; fentanyl 0.75 µg kg^{-1} was given 5 min before induction. Twenty patients were then allocated randomly to receive the minimum mean induction dose of propofol from the above groups (0.82 mg kg^{-1}) at 150 ml h^{-1} or as a bolus over 5 s to compare bolus with infusion administration. No further drug was given for an observation period of up to 200 s, with additional increments as required after that time. Arterial pressure and heart rate were recorded at the end of induction and 2, 5 and 10 min later. Statistical analysis was by ANOVA or chi-square.

There were significant differences in induction dose between the three initial infusion rates (table IX). In the comparison of 150-ml h^{-1} infusion and bolus, there were no differences in arterial pressure or heart rate for any of the groups. Anaesthesia was successfully induced in all of the bolus group and eight of the infusion group. There were significant differences ($P < 0.05$) in the induction time between the bolus group (38 (SD 14) s) and the infusion group (159 (4) s) (table IX).

Induction of anaesthesia with propofol may be achieved with smaller doses than reported previously if adequate time for circulation of drug is permitted. The appropriate doses may be calculated from infusion induction studies.

TABLE IX. *Mean doses of propofol and induction times after infusions of 600, 300 or 150 ml h^{-1}, set infusion of 0.82 mg kg^{-1} at 150 ml h^{-1} or set bolus administration of 0.82 mg kg^{-1} over 5 s*

Rate (ml h^{-1})	Mean dose (mg kg^{-1})	Time (s)
600	1.65 (0.19)	69.4 (3.2)
300	1.22 (0.08)	102.3 (7.5)
150	0.82 (0.04)	140.1 (6.9)
Bolus (set)	0.82	38.5 (14.4)
Infusion (set)	0.82	159.3 (4.4)

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COMPARISON OF THIOPENTONE AND PROPOFOL AT TWO RATES OF ADMINISTRATION IN PATIENTS WITH SEVERE HEAD INJURY

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Post-traumatic intracranial hypertension may respond well to hypnotic therapy, but it remains unclear if the rate of administration influences efficacy. This study compared the effects of rapid (20 s) and slow (120 s) infusions of propofol 1.5 mg kg^{-1} and thiopentone 4 mg kg^{-1} administered into a central vein, on cerebral perfusion pressure (CPP) and jugular bulb oxygen saturation (Sj_{O_2}). We studied 10 normovolaemic patients with severe head injury (post resuscitation admission Glasgow coma score less than 9) with untreated normal intracranial pressure (ICP). Patient's lungs were ventilated artificially to hypocapnia (Pa_{CO_2} 3.5–4.0 kPa); a standard regimen of management was applied. Arterial pressure (AP), ICP, arterial oxygen saturation (Sp_{O_2}) (by pulse oximetry), Sj_{O_2} (Oximetrix 3), end-tidal carbon dioxide concentration and cerebral electrical activity (cerebral function monitor) were recorded continuously. Following informed consent by a relative, each patient was studied on four occasions according to a structured randomized code. Physiological variables were recorded before hypnotic infusion and thereafter for 30 min or until return to baseline values.

Within and between drug infusion differences were analysed by paired Wilcoxon test or paired Student's t test. Comparison was made between methods of administration of each drug and effects of each drug given by the same method.

By rapid infusion, propofol caused a significantly greater decrease in mean AP (33 (SD 3.7) mm Hg) compared with thiopentone (24 (8) mm Hg) ($P < 0.001$). Reduction in ICP was similar in both groups (thiopentone 9.6 (2.8) mm Hg; propofol 6.8 (3.0) mm Hg). Decrease in CPP was greatest in the propofol group (28 (5) mm Hg, compared with 19 (5.6) mm Hg for thiopentone (ns)). Sj_{O_2} decreased significantly more in the propofol group over 30 min ($P < 0.001$); the maximum decreases in mean Sj_{O_2} were similar (propofol 11 (4.8)%; thiopentone 12 (11)%).

By slow infusion, propofol caused a significantly greater decrease in mean AP than thiopentone (29.7 (4) mm Hg cf. 21 (5.7) mm Hg ($P < 0.001$)). Maximum reductions in ICP were similar (thiopentone 6 (3) mm Hg; propofol 5.7 (4) mm Hg). Decrease in CPP was greatest in the propofol group (propofol 26.6 (3.2) mm Hg; thiopentone 18 (6) mm Hg ($P < 0.001$)). Maximum decreases in Sj_{O_2} were similar in both groups (propofol 6.4 (4)%; thiopentone 7 (3.6)%); however, over 30 min Sj_{O_2} was significantly less in the propofol group ($P < 0.001$).

Comparing rapid with slow infusion of propofol, rapid infusion caused a greater decrease in mean AP (ns). Maximum reduction in ICP and CPP was similar in both groups, but over 30 min CPP was significantly less in the rapid infusion group ($P < 0.05$). The decrease in Sj_{O_2} was significantly greater in the rapid infusion group ($P < 0.001$).

Comparing rapid with slow infusion of thiopentone, rapid infusion caused a greater decrease in mean AP (ns). Reduction in ICP was greatest in the rapid infusion group ($P < 0.001$). The maximum decrease in CPP was similar in the two groups but, over 30 min, decrease in CPP was greater in the rapid infusion group ($P < 0.001$). Decrease in Sj_{O_2} was greatest in the rapid infusion group ($P < 0.001$).

Although all four treatments led to a decrease in ICP, CPP and Sj_{O_2} were compromised. CPP and Sj_{O_2} were affected least adversely and recovered most rapidly in the slow infusion thiopentone group, exceeding pretreatment values in eight of 10 patients. In the treatment of intracranial hypertension after severe head injury, hypnotic drugs should be infused slowly, with continuous monitoring of CPP. Thiopentone by slow infusion appears superior to propofol.

EFFECT OF 5% AND 10% MAC OF CYCLOPROPANE AND HALOTHANE ON PEAK VELOCITY OF SACCADIC EYE MOVEMENTS

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Saccadic eye movements, the fastest voluntary movement of which the human motor system is capable, are a sensitive indicator of CNS depression. In a previous study by Gao, Marshall and Vickers [1] 5% and 10% MAC of isoflurane were found to depress the peak velocity of saccadic eye movements (PSV), whereas equi-MAC concentrations of nitrous oxide were indistinguishable from air. One hypothesis to explain the difference between the agents is the sympathetic stimulating effect of nitrous oxide. Cyclopropane also has a stimulating effect and it seemed worthwhile to compare its effects with those of halothane, an agent similar to isoflurane.

Six healthy volunteers were studied. Each wore an R.A.F. face mask with non-rebreathing valves. Inspired concentrations of agents were adjusted to maintain the desired end-tidal concentration using the Narkup computer program by Lockwood and White [2] adjusted for the subject's age, sex, height and body weight. Alveolar gas samples were taken from the mask through a fine-bore tube sampling at 10-min intervals. End-tidal cyclopropane and halothane concentrations were measured by gas chromatography.

Saccades were generated by having the subject follow the movements of an illuminated target. Eye position was monitored from the electro-oculogram (EOG), which was measured between two silver–silver chloride electrodes placed on the outer canthi of each eye and an indifferent electrode placed on the forehead. A microcomputer controlled the target movements, digitized the EOG and stored the data. Saccade analysis was carried out according to the method of Marshall and Richens [3].

Each volunteer received cyclopropane, halothane or air in random order on different days at the same time of the day. Each session started with a 15-min baseline breathing air, 30 min each of 5% and 10% MAC and 10 min of recovery breathing air. Saccadic eye movements were measured at 10-min intervals throughout. An additional measurement was taken 15 min after removal of the mask. The values at 15 and 25 min for each concentration of anaesthetic were averaged and the means compared with control air values by Student's two-tailed paired t test. Each volunteer was asked to rate their alertness by visual analogue scale before each eye movement measurement; the ratings were analysed by the Wilcoxon test.

End-tidal concentrations of cyclopropane at 15 and 25 min during the inhalation periods were mean 4.7 (SEM 0.28) % and 8.8 (0.85)% of MAC; those of halothane were 5.3 (0.46)% and 9.3 (0.46)% of MAC, respectively. The currently accepted MAC values of 0.76% for halothane and 9.2% for cyclopropane were assumed. Highly significant depression in PSV ($P < 0.01$) was found with both concentrations of cyclopropane and halothane when compared with air. Depression of PSV by halothane was significantly greater ($P < 0.05$) than that by cyclopropane at each concentration and at the grand mean concentration, 7.04 (0.50)% of MAC, calculated from all the concentrations of both agents at 15 and 25 min. PSV had returned to baseline value 5 min after discontinuation of the agents. There was no significant difference between air, cyclopropane and halothane at either concentration in subjective assessment of sedation.

Our results indicate that 5% or 10% MAC concentrations of cyclopropane and halothane do not reduce PSV equally; cyclopropane is intermediate between nitrous oxide and halothane, which had very similar effects to those of isoflurane, reported previously by Gao, Marshall and Vickers [1].

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PERIPARTUM CHANGES IN GASTRIC EMPTYING

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Inhalation of gastric contents is an important cause of anaesthetic mortality associated with obstetrics [1] and delayed gastric emptying may increase its likelihood. There is conflicting evidence regarding the effect of pregnancy and the immediate postpartum period on gastric emptying.

Serial measurements of gastric emptying in the same patient comprise the most satisfactory methods, but repeated x-ray and scintigraphic investigations are unethical. The effect of pregnancy on paracetamol pharmacokinetics may render this method inaccurate.

Applied potential tomography (APT) is a safe, repeatable and reliable method of measuring gastric emptying [2], and we have used this technique in pregnant patients.

We studied healthy patients taking no medication and undergoing normal pregnancy and delivery. All gave written informed consent. Ethics Committee approval for the study was obtained.

APT measures gastric emptying by computing changes in resistivity of gastric contents as the stomach empties. Before the investigation, it is necessary to administer a histamine type-2 blocker to inhibit gastric acid production which may affect resistivity readings.

Gastric emptying was measured at 37–40 weeks gestation, 2–3 days postpartum and after final postpartum assessment at 6 weeks (control). On each occasion, the patient was starved for 4 h and ranitidine 150 mg was taken orally 2 h before the study. Gastric emptying of distilled water 400 ml was then measured by APT. Data were collected at 1-min intervals and time to 50% emptying (TE_{50}) was calculated (table X).

TABLE X. *Individual TE_{50} for the first nine patients studied*

Patient No.	TE_{50} (min) 37–40 weeks gestation	2–3 days postpartum	Control
1	15	6	12
2	14	6	13
3	8	12	15
4	25	9	12
5	26	6	13
6	14	18	12
7	11	5	
8	16	22	
9	11	16	

These provisional data show that control values for gastric emptying were consistent between patients. Changes in the peripartum period were inconsistent. Gastric emptying was relatively delayed in two patients before delivery.

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USE OF BUCCAL PROCHLORPERAZINE IN THE PREVENTION OF POSTOPERATIVE SICKNESS

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Controversy exists regarding the routine prophylactic use of antiemetics [1]. With the increase in day-case surgery, there is an expectation that postoperative sickness will increase because of early mobilization and fluid challenge [2]. Recently, prochlorperazine in a form for buccal administration has been introduced. The objectives of this study were to examine buccal prochlorperazine as an antiemetic administered before operation.

Fifty-two patients (ASA I or II) admitted for minor gynaecological surgery or breast biopsy were included in the study. Patients were allocated randomly to one of two groups: group 1 were given no preoperative antiemetic; group 2 received buccal prochlorperazine 6 mg 1 h before operation. Nausea was assessed on a visual analogue scale. Assessments were made before operation (baseline) and 1, 4 and 24 h after operation. The 24-h assessment was by telephone, at which time the patients were asked also about vomiting, retching, sedation, headache and anaesthetic preference for future surgery.

Patients were unpremedicated and received fentanyl 1 µg kg^{-1} before induction of anaesthesia with propofol

2–3 mg kg^{-1}. All patients breathed spontaneously, apart from those undergoing laparoscopic tubal ligation, who received mechanical ventilation of the lungs with 66% nitrous oxide and 0.5–1% isoflurane in oxygen. Atracurium was used to provide neuromuscular block.

Statistical analysis included the Kruskal–Wallis and chi-square tests.

Type of surgery and patient characteristics were similar between the two groups. Overall, 57.7% of patients in group 1 and 15.4% of patients in group 2 experienced nausea at one or more of the assessment times ($P < 0.05$). The greatest incidence of nausea occurred 1 h after recovery Of the patients who experienced nausea, 86.7% in group 1 and 50% in group 2 described it as mild in nature. Vomiting occurred in 26.9% of group 1 and 3.8% of group 2 patients. Postoperative requirements for opioid drugs were similar between the groups.

We were surprised to find that the incidence of severe nausea in this study was small and that most patients did not require treatment for nausea that they described as mild in nature. Propofol, when used for induction of anaesthesia, is said to have antiemetic properties and this may account for the low incidence of moderate to severe nausea seen in this study [3].

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RELATIONSHIP OF POSTOPERATIVE AND CANCER CHEMOTHERAPY SICKNESS

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In a survey of the frequency and severity of sickness following moderately emetic cancer chemotherapy [1], it was noted that 139 of 141 patients had received a recent general anaesthetic for a non-abdominal operation. Full details of anaesthesia had been recorded and patients were questioned about sickness in the first 2 days after operation. The frequency of sickness (nausea, vomiting, or both) on these two occasions has been compared, and data analysed to determine if patients who experience postoperative sickness are susceptible to chemotherapy sickness.

Non-opioid premedication was followed by a barbiturate–fentanyl–halothane sequence with suxamethonium as required.

In general, women are more susceptible to postoperative sickness than men. This was confirmed in the present series and shown to apply to chemotherapy-induced sickness: 23% of 100 women had postoperative sickness compared with 7% of 39 men; the comparable figures for cancer chemotherapy were 78% and 46%. This sex difference was significant in both series ($P < 0.01$).

Because only three men were sick after operation, study of the relation of postoperative and chemotherapy sickness was limited to women. In table XI, chemotherapy sickness is graded as described elsewhere [2].

TABLE XI. *Number of women with chemotherapy-induced sickness after receiving moderately emetic drugs, related to history of postoperative sickness*

	History of postop. sickness?	
	Yes ($n = 23$)	No ($n = 77$)
Chemotherapy sickness		
Nil	2	20
Slight	2	15
Moderate	8	29
Marked	11	13

The relationship was significant for patients with a history of postoperative sickness, who more frequently had severe sickness after chemotherapy ($\chi^2 = 10.72$; df $= 3$; $P = 0.033$).

With the introduction of ondansetron, chemotherapy sickness is no longer a major problem. However, budget limitations may restrict its use to patients who are particularly susceptible to sickness. This includes women with a previous history of postoperative nausea or vomiting who are prescribed a course of drugs with a moderate emetic potential. The present conclusions do not apply to highly emetic drugs, such as cisplatin, which cause sickness in 90–95% of patients [2].

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DOSE REQUIREMENTS TO SUPPRESS CONSCIOUSNESS BY CONTINUOUS INFUSION OF PROPOFOL IN YOUNG ADULTS

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Previous studies have defined the dose requirements for infusions of propofol, in combination with alfentanil, using quantal somatic motor responses [1] or lower oesophageal contractions [2] as indices of adequacy of anaesthesia. To extend this information, and to define the dose requirement to ensure loss of consciousness, we have used a three-stage infusion scheme [3] to establish blood concentrations of propofol in a range covering wakefulness, sedation and anaesthesia as defined by loss of consciousness and suppression of the eyelash reflex.

Fifty-two unpremedicated ASA I patients, aged 18–40 yr, were allocated to one of five groups to receive a loading dose

TABLE XII. *Scheme for administration of propofol*

	Group				
	A	B	C	D	E
Loading dose (mg kg^{-1})	0.5	0.6	0.75	0.9	1.0
Infusion I (mg kg^{-1} h^{-1})	5.0	6.0	7.5	9.0	10.0
Infusion II (mg kg^{-1} h^{-1})	4.0	4.8	6.0	7.2	8.0

of propofol, and a three-stage infusion scheme (table XII). At 10 and 20 min after the loading dose, patients were asked to respond to verbal command and, depending on their response, they were subjected to other sensory stimuli and their voluntary or reflex responses noted. The data were subjected to probit analysis (SAS software package).

The ED$_{50}$ for the final infusion rate of propofol to abolish consciousness (loss of response to verbal command) was 4.79 (95% confidence limits (CL) 4.25–5.45) mg kg^{-1} h^{-1}; ED$_{95}$ was 7.49 (95% CL 6.27–12.28) mg kg^{-1} h^{-1}. The dose–response curve for loss of the eyelash reflex was almost identical to that for loss of response to verbal command, giving ED$_{50}$ and ED$_{95}$ values of 4.98 and 7.15 mg kg^{-1} h^{-1}, respectively.

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COMPARISON OF LARYNGEAL MASK AIRWAY WITH TRACHEAL INTUBATION FOR INTRAOCULAR SURGERY

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Tracheal intubation is associated with pressor responses, straining, coughing, breath-holding and increase in intraocular pressure. We investigated the usefulness of the laryngeal mask airway (LMA) as an alternative to a tracheal tube for day-case intraocular surgery.

Thirty patients (ASA I, II and III) having cataract extraction under general anaesthesia were allocated randomly to two groups: LMA was used in group L and a tracheal tube in group E. Temazepam 20 mg was given orally 90 min before operation. Intraocular pressure was measured before and after the induction of anaesthesia and 1 min after application of the mask or insertion of the tube. Anaesthesia was induced and maintained with a propofol infusion and 60% nitrous oxide in oxygen. Propofol was discontinued at the insertion of the last corneal stitch and neuromuscular block was antagonized. Eye bandage was applied and removal of the mask or tracheal tube was carried out on re-establishment of spontaneous breathing. Coughing, straining and breath-holding were recorded. Student's *t* and chi-square tests were used for statistical analysis of the data.

TABLE XIII. *Intraocular pressures (mean (SD)) related to the use of laryngeal mask airway (LMA) or a tracheal tube (TT) during intraocular surgery*

	LMA ($n = 15$)	TT ($n = 15$)
Before induction	14.0 (4.6)	12.7 (2.8)
After induction	8.6 (4.2)	7.4 (3.4)
After airway placed	8.6 (4.4)	8.1 (3)

The difference in intraocular pressure between the groups, or in the same group before and after application of LMA or insertion of the tracheal tube were not significant (table XIII). Eighty-seven percent of the intubated patients coughed and 47% held their breath at extubation, while no patient coughed or held breath in the LMA group ($P < 0.05$). Thirty-three percent of the patients in group E, but no patient in group L, reported sore throat ($P = 0.02$).

The demand for operations such as cataract extraction is growing with the number of elderly people in the community. Intraocular day-case surgery does not increase perioperative morbidity [1], and more patients can be treated. We did not find significant increases in intraocular pressure following use of the LMA or a tracheal tube. Successful use of LMA for controlled mechanical ventilation has been reported [2]; we did not experience any difficulty.

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MIDAZOLAM AND PROPOFOL FOR INDUCTION OF ANAESTHESIA

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A synergistic interaction has been demonstrated between midazolam and thiopentone when administered for induction of anaesthesia [1]. The possibility of an interaction between midazolam and propofol at induction of anaesthesia was investigated in this study.

After Ethics Committee approval was obtained, informed consent was obtained from 140 otherwise healthy patients (18–55 yr; 50–82 kg body weight) admitted for elective gynaecological surgery. All patients were unpremedicated and not receiving any psychoactive therapy. They were assigned randomly to groups of 10, to receive propofol 0.4, 0.8, 1.2, 1.6, 2.0, 2.4 or 2.8 mg kg^{-1}, or midazolam 0.1, 0.13, 0.16, 0.22, 0.28, 0.34 or 0.4 mg kg^{-1} via an antecubital fossa vein over 20 s. Three minutes after administration of midazolam or 1 min after propofol, a blinded observer recorded any loss of response to command, loss of eyelash reflex and toleration of 66% nitrous oxide and 1% isoflurane in oxygen via a face mask for 30 s. Anaesthesia was then continued as appropriate for surgery.

ED$_{50}$ values for midazolam and propofol were obtained and an additional 92 similar patients received one of nine appropriate drug combinations of midazolam and propofol (10 or 11 patients per group). Midazolam 0.03, 0.06 or 0.12 mg kg^{-1} was injected, followed 2 min later by propofol 0.3, 0.6 or 0.9 mg kg^{-1}. Loss of response to command was assessed by the same blinded observer 1 min after injection of propofol. The results were subjected to probit analysis [2].

The ED$_{50}$ value (95% confidence interval) based on the end-point loss of response to command for propofol was 1.24 (0.94–1.48) mg kg^{-1} and that for midazolam 0.25 (0.15–0.5) mg kg^{-1}. The clinical responses were not well described by the additive probit model, but the model specifying an interaction between the drugs described the responses significantly better ($\chi^2 = 16.6$, df = 1, $P < 0.001$). A range of predicted ED$_{50}$ values was obtained for the drugs given in combination, for example: midazolam 0.03–propofol 0.8 mg kg^{-1}; midazolam 0.06–propofol 0.59 mg kg^{-1}.

A synergistic interaction was demonstrated between low dose midazolam and propofol at induction of anaesthesia. Twenty-five percent ED$_{50}$ midazolam followed by 50% ED$_{50}$ propofol produced the same clinical response as the ED$_{50}$ of either drug given alone. The mechanism for this interaction is as yet unknown.

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ARTERIAL PRESSURE RESPONSES INDUCED BY STIMULI TO THE UPPER AIRWAY IN ANAESTHETIZED PATIENTS

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The cardiovascular response to intubation has been studied extensively [1]. In anaesthetized animals, light stimuli to the upper pharyngeal surface and nasal, laryngeal and tracheobronchial mucosa result in an increase in arterial pressure [2]. The exact stimuli and airway regions responsible for the cardiovascular response in man are not clear.

We have studied 64 patients, ASA I and II, mean age 32.3 yr (range 17–60 yr), undergoing gynaecological and minor ENT procedures, with no history of hypertension and receiving no cardiac medication. They were allocated randomly to groups of from 5 to 7 individuals to receive one of 11 different stimuli (table XIV). Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v. given over 20 s, with additional bolus doses of 50 mg as required to obtain loss of eyelash reflex (total dose 5–8 mg kg^{-1}) and, where indicated, suxamethonium 100 mg i.v. Each stimulus was applied 20 s after the eyelash reflex was lost and was maintained for 20 s. In those patients who received suxamethonium, the stimulus was given at the end of muscle fasciculation. Systolic arterial pressure recordings were made from a middle finger using a continuous plethysmographic method (Ohmeda Finapres). The maximum change in arterial pressure was calculated relative to the pressure at the time of stimulus application or injection of suxamethonium.

TABLE XIV. *Changes in systolic arterial pressure (SAP) in relation to 11 stimuli applied to the subject (mean (SEM))*

	Stimulus	Max. change in SAP (mm Hg)
1.	None	5 (3)
2.	Jaw opening and neck extension	20 (7)
3.	Wood on oropharynx	4 (5)
4.	Metal on uvula	14 (2)
5	Guedel airway No. 2	7 (3)
6.	Guedel airway No. 4	19 (7)
7.	Laryngoscope at base of tongue	8 (2)
8.	Suxamethonium	32 (7)
9.	Suxamethonium + laryngoscope blade anterior to epiglottis	72 (11)
10.	Suxamethonium + laryngoscope blade posterior to epiglottis	88 (4)
11.	As No. 9, with intubation	110 (7)

In contrast to animal responses [2], a marked hypertensive response occurred only after stimulation of the larynx and epiglottis (table XIV). Stimulation of oral and pharyngeal structures caused no clinically important increase in arterial pressure. Suxamethonium alone increased arterial pressure markedly. These patients were anaesthetized with thiopentone, however, which may cause less suppression of reflex response than volatile anaesthetics [1].

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RESTING ENERGY EXPENDITURE IN CHILDREN WITH LIVER DISEASE

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Increased resting energy expenditure may contribute to impaired growth in children with chronic liver disease [1]. This study compared oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) in children with chronic liver disease and failure to thrive with an age-matched control population.

Indirect calorimetry with an open canopy technique was used [2]. Liver disease presented as jaundice, ascites, hepatomegaly and abnormal liver function tests or clotting screen. Failure to thrive was defined as weight of triceps skinfold thickness decreasing from a previously maintained growth centile by at least 1 SD for more than 3 months or longer. There were 24 children with liver disease and failure to thrive (mean age 4.1 yr (range 0.11–14 yr), mean weight 14.5

(SEM 2.6) kg) and 25 control children (mean age 4.5 yr (range 0.13–12 yr), mean weight of 19.2 (2.4) kg).

All studies were performed at least 2 h after a meal. Babies younger than 1 yr were studied while lying on their mother's lap; older children were encouraged to watch cartoons while sitting in a video box wearing a flow hood. These techniques were well tolerated. $\dot{V}O_2$ and $\dot{V}CO_2$ were measured continuously using a mass spectrometer. A small volume hood and flow rate of 60 litre min^{-1} ensured rapid equilibration and enabled measurements to be completed within 10 min.

The mean (SEM) resting $\dot{V}O_2$ in the control group was 8.5 (0.72) ml kg^{-1} min^{-1}; $\dot{V}CO_2$ was 7.3 (0.58) ml kg^{-1} min^{-1}. Children with liver disease demonstrated a highly significant increase in $\dot{V}O_2$ and $\dot{V}CO_2$ (means 12.1 (1.1) ml kg^{-1} min^{-1} and 10.4 (0.82) ml kg^{-1} min^{-1}, respectively ($P < 0.01$)).

Children with chronic liver disease have a high resting oxygen consumption which may contribute to their failure to thrive. The mechanism of the increased $\dot{V}O_2$ and $\dot{V}CO_2$ is not known, but the implication for the anaesthetist is that desaturation will occur more quickly.

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POSTER PRESENTATIONS

ANAESTHETIC–PLASMA INTERACTIONS: A STUDY USING NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY (MRS)

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General anaesthetics probably exert their effects through interactions with lipids, proteins, or both. The correlation of anaesthetic potency with lipid solubility suggests that the critical site(s) have hydrophobic properties (e.g. membrane lipids or hydrophobic protein domains). Previous studies have investigated interaction between proteins and anaesthetics using model systems such as haemoglobin [1]. Wyrwicz and colleagues demonstrated two sites where halothane binds in blood—red cells and plasma [2]. We are studying *in vitro* changes in spectra using ^{1}H-NMR following addition of halothane and thiopentone to human and rabbit plasma.

In vitro additions of halothane 1–50 µl or thiopentone 25–1000 µg were titrated into 600-µl aliquots of plasma. ^{1}H-NMR spectra were recorded at 298 K on a 500-MHz AM Bruker spectrometer (NIMR, Mill Hill) [3].

Halothane caused lipid mobilization, with significant sharpening of peaks assignable to the methyl groups of cholesterol, and the $—CH_3$ and $—CH_2$ groups of fatty acids. There was little change in the intensity of the choline head group peaks. The effects were observed with concentrations of halothane 15 mmol litre^{-1} (clinical concentrations: 1–4 mmol litre^{-1}); further additions enhanced the spectral changes.

Addition of thiopentone $\leqslant$ 400 µmol litre^{-1} had little effect on the lipid region of the spectrum; greater concentrations (7–8.5 mmol litre^{-1}) increased the signal intensity of free metabolites (especially lactate).

Increased metabolite signals and some evidence of lipid mobilization were observed in preliminary data using samples obtained during halothane–oxygen anaesthesia (inspired concentrations 1–3.5% (1–4 mmol litre^{-1})) in the rabbit. During thiopentone anaesthesia, only minimal changes were observed. Plasma samples obtained from anaesthetized patients did not show the same spectral effects.

These data indicate increased mobilization of lipids in lipoproteins following additions of halothane, while thiopentone primarily affected plasma proteins.

ACKNOWLEDGEMENTS

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HYPERVENTILATION AND BLOOD CONCENTRATIONS OF PROPOFOL DURING TOTAL I.V. ANAESTHESIA

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Many studies of propofol anaesthesia have indicated a high degree of intra- and inter-patient pharmacokinetic variability [1]. Ventilatory conditions during the maintenance of anaesthesia may alter haemodynamics and acid–base balance [2], and could affect the distribution and elimination of propofol. We have compared the effects of hypocapnia and eucapnia on blood concentrations of propofol in patients receiving propofol infusions.

The study was approved by the local Ethics Committee and written, informed consent was obtained. Ten male patients classed ASA I, of comparable age, weight and of medium build, having inguinal hernia repair, were allocated randomly to have the lungs ventilated to either hypocapnia (group H) or eucapnia (group N). All patients were premedicated with temazepam 20 mg 90 min before operation. Anaesthesia was induced with alfentanil 50 µg kg^{-1} and propofol 1 mg kg^{-1} (time 0) and maintained with alfentanil 50 µg kg^{-1} h^{-1} and propofol 10 mg kg^{-1} h^{-1} for 10 min, 8 mg kg^{-1} h^{-1} for 10 min, and 6 mg kg^{-1} h^{-1} thereafter. Suxamethonium 1 mg kg^{-1} was given to facilitate tracheal intubation. The patient's lungs were ventilated with oxygen enriched air ($F\text{I}_{O_2}$ 0.3), controlled initially by hand via a Mapleson D breathing system and subsequently by a Penlon "Oxford" ventilator set to deliver a tidal volume of 10 ml kg^{-1} at a rate of 10 b.p.m. This achieved a $P\text{E}'_{CO_2}$ of 3.5 kPa in group H and, by the addition

TABLE XV. *Mean* (SD) *whole blood concentrations of propofol for the two groups*

Time (min)	Propofol concn (μg ml^{-1}) Group N ($n = 5$)	Propofol concn (μg ml^{-1}) Group H ($n = 5$)
2	4.66 (0.92)	4.25 (1.51)
5	4.41 (1.01)	4.26 (1.34)
10	5.24 (1.16)	3.75 (0.76)
20	5.12 (0.76)	4.15 (1.02)
30	4.34 (0.41)	3.57 (0.83)
40	4.08 (0.18)	3.61 (0.72)
50	3.93 (1.51)	3.04 (0.48)

of carbon dioxide to the inspired mixture, $P_{E'_{CO_2}}$ 5.5 kPa in group N.

Arterial blood was sampled at 2, 5, 10 min after induction of anaesthesia and subsequently at 10-min intervals until the end of surgery, for measurement of whole blood concentrations of propofol by HPLC and blood-gas tensions.

Arterial blood-gases taken at 40 min gave a mean Pa_{CO_2} of 5.53 (SD 0.98) kPa in group N and 3.34 (0.42) kPa in group H. Corresponding values for pH were 7.36 (0.06) and 7.52 (0.05).

Although the blood propofol concentrations were consistently smaller in the hypocapnic patients (table XV), there were no significant differences between the two groups at any time.

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TOTAL I.V. ANAESTHESIA WITH PROPOFOL AND ALFENTANIL: INFLUENCE OF AGE AND WEIGHT ON DOSE REQUIREMENTS

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Data from previous research [1–3] carried out in this department were analysed in an attempt to provide a unified multivariate probit model of the dose requirements for propofol during total i.v. anaesthesia in patients of different ages. A total of 206 patients having body surface surgery were studied. Anaesthesia was by infusions of alfentanil 50 μg kg^{-1} h^{-1} (in children, 65 μg kg^{-1} h^{-1}) and propofol in a stepped infusion designed to achieve and maintain a designated blood concentration of propofol within 5 min of induction. At the time of incision, presence or absence of gross spontaneous somatic movement was noted.

Data were submitted to a multivariate probit analysis program (SAS for PC, version 6.03), in order to determine the parameter estimates for the determinants of the probability of movement in response to surgical stimulation during anaesthesia. Variables submitted included the final infusion rate of propofol administered, calculated in mg kg^{-1} h^{-1} and other powers of body weight, and age of patient, also in various powers. Probit models were fitted to a normal, a logistic or a Gompertz distribution. The goodness of fit was tested using Pearson and Likelihood Ratio chi-square tests, and the significance of each parameter estimate in the final probit model was tested with a chi-square test.

When the administered dose (mg kg^{-1} h^{-1}) was submitted to analysis, it was found that body weight made an additional significant contribution to the final probit model. If the dose was calculated as mg kg$^{-0.75}$ h^{-1}, the goodness of fit of the final model was improved and other functions of body weight no longer contributed. Similarly, the square root of age made a significant contribution to the model, and when this was included it was not necessary to include any other function of age.

The final probit regression model was as follows:
If P is the probability that a patient will not move in response to surgical incision, *Dose* is the final infusion rate (mg kg$^{-0.75}$ h^{-1}) and *Age* is the patient's age (yr), then:

$$\text{Probit}\ (P) = -7.28 + 5.74 \log_{10}\ (\mathit{Dose}) + 0.31\ \mathit{Age}^{0.5}$$

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SEDATION WITH PROPOFOL DURING SURGERY UNDER REGIONAL BLOCK: EVALUATION OF A COMPUTER CONTROLLED INFUSION SYSTEM

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Sedation is used frequently for patients undergoing surgery with regional block. Propofol administered by continuous i.v. infusion has been shown to produce satisfactory sedation in this situation [1], although rapid alterations in sedation level in response to changing patient requirements may not be easy to achieve by manual adjustment of the infusion rate.

The successful use of a pharmacokinetic model-based, computer-driven propofol infusion for general anaesthesia has been described recently by White and Kenny [2]. This infusion system allows the user to select a desired target blood concentration of propofol, which is achieved by an initial loading dose and then maintained by a varying infusion which is calculated by a pharmacokinetic algorithm. Satisfactory correlation between predicted and measured concentrations of propofol was reported in patients undergoing general anaesthesia [2].

We have evaluated a modification of this system, based on an Ohmeda 9000 syringe pump and Psion Organiser, for intraoperative sedation in 20 patients undergoing lower limb surgery with spinal anaesthesia. Initial target blood concentration was selected between 1.0 and 1.5 μg ml^{-1} and adjusted throughout the procedure according to patient requirements. Sedation was commenced after the spinal block was established satisfactorily, and was assessed regularly by the anaesthetist using the following five-point sedation score [3]:

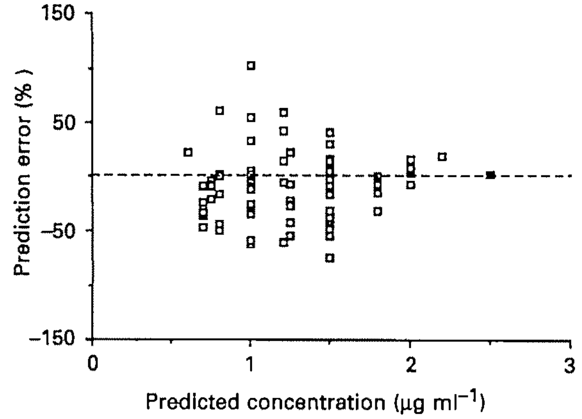

FIG. 5. Relationship between predicted and measured blood concentrations of propofol infused by a computer controlled system.

1 = awake; 2 = drowsy with eyes open; 3 = eyes closed, but rousable to speech; 4 = rousable to mild physical intervention; 5 = unrousable. The clinical performance of the system was assessed in terms of the percentage time spent at the target sedation scores of 3 or 4 and the performance of the pharmacokinetic algorithm was assessed by comparison between predicted and measured blood concentrations of propofol.

Satisfactory performance of the system in this situation is suggested by the fact that 88% of the total steady state time for all the patients was spent at the target sedation scores of 3 or 4.

The relationship between predicted and measured blood concentration of propofol is shown in figure 5. The mean prediction error for this relationship is −6.8%, with a precision of 25.2%. This correlation compares favourably with that found when using the system for general anaesthesia [2]. In addition, the median measured blood concentration of propofol required for satisfactory sedation was 1.1 µg ml^{-1} (range 0.4–2.6 µg ml^{-1}).

This study demonstrates that satisfactory intraoperative sedation may be obtained at blood concentrations of propofol between 0.4 and 2.6 µg ml^{-1}, and that this may be safely and easily achieved and controlled using this computer based infusion system.

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RESUSCITATION TRAINING FOR THE OPERATING DEPARTMENT

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The use of mannequins for training in basic cardiopulmonary resuscitation has become routine, and currently available models provide sophisticated feedback on performance. The mannequin is commonly placed on a low, firm surface providing optimal conditions for performing external cardiac compression (ECC); however, a patient suffering cardiac arrest within the operating department will be on a relatively high, soft surface. Vickers [1] has postulated that failure to resuscitate children may have been related to the operating table mattress construction, and we are aware of two instances in which obese patients have been inadequately resuscitated in theatre. We investigated the ability of medical students to transfer newly acquired skill in ECC from the training situation to an operating theatre simulation.

Thirty-three medical students received individual instruction in ECC using a mannequin with visual feedback and recording facility (Laerdal Skillmeter Resusci Anne). The mannequin was placed on a firm surface adjusted to a comfortable height for each individual. When competence had been attained with visual feedback, a record was made of 60 s of continuous ECC performed without visual feedback. Recordings were repeated whilst each subject performed a further 60 s of ECC after an interval of approximately 30 min, the surface being at 84 cm (common minimum operating table height) and covered with an operating table mattress. The mannequin registers a compression depth between 38 and 52 mm as correct; 80% correct depth compressions was regarded as satisfactory. The subject's height and sex were noted.

Nine of the subjects were female and 24 male. Nineteen (58%) were successful immediately after initial training. In the operating table simulation, only eight (24%) were successful (chi-square 13.3, $P < 0.001$). Of these, five had been initially successful and three had not. These proportions (26% and 21%) are similar. After initial training, five female subjects and 14 males were successful (55% and 58%); in the operating table simulation one female and seven males were successful (13% and 29%). Neither of these proportions is significantly different ($\chi^2 = 0.021$, 1.16; $P = 0.9$, 0.3, respectively); however, when the numbers of satisfactory compressions achieved by males and females during the operating table simulation were compared, males were significantly better (mean 46.0 *vs* 12.8, $P < 0.05$, unpaired *t* test). The relation between subject height and percentage of satisfactory compressions was examined by calculating regression. No significant association was found after initial training ($r = 0.11$, $P = 0.5$). However, in the operating table simulation, height was positively related to success ($r = 0.39$, $P < 0.05$). Females were significantly shorter than males (mean difference 11.2 cm, $P < 0.001$). No subject less than 170 cm was successful in the operating table simulation.

It was disappointing that 42% of our subjects were unable to reproduce a satisfactory standard immediately after initial training. However, the 14 mm acceptable range for compression depth is exacting and, in practice, effective cardiac output may be achieved by compressions on either side of this range. The results also suggest that ECC training in one set of circumstances is not easily transferred and that successful resuscitation in the operating theatre may be compromised as a result. The nature of the surface on which the patient is placed and its height from the ground may be important factors which should be taken account of during cardiopulmonary resuscitation training and real resuscitation attempts. The platforms available in operating theatres to aid short people are also necessary in recovery rooms, where trolleys are commonly higher than operating tables and are too narrow to allow staff to kneel alongside the victim during ECC.

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POST-POST-TETANIC FACILITATION FADE (PPTFF)

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Post-tetanic facilitation is a well described feature of non-depolarizing neuromuscular block. The term refers to a transient improvement in neuromuscular transmission that follows a period of tetanic stimulation. As the improvement decays, neuromuscular block returns to its previous time course, and is generally thought to do so without overshoot. We report that the decay of post-tetanic facilitation may sometimes be followed by a depression of transmission to less than what is expected from the background time course of neuromuscular block.

In patients who had consented to neuromuscular monitoring, a Datex Relaxograph was used to monitor train-of-four responses of the first dorsal interosseous muscle of the hand, with stimuli being applied to the ulnar nerve at the elbow. A second set of surface stimulating electrodes was attached over the same ulnar nerve at the wrist so that 50-Hz bursts of suxamethonium tetanic stimuli could be applied by a separate peripheral nerve stimulator (Bard, model 750 digital). A "tetanic challenge" consisted of a sequence of five bursts, spread as evenly as possible throughout a selected 18-s interval between the trains-of-four delivered by the Relaxograph, with each burst lasting about 1 s. Tetanic challenges were repeated at intervals of at least 7 min during the time course of recovery from non-depolarizing block that depressed the first twitch of the train-of-four (T1) to less than 10% of control.

Early in the recovery, before the T4/T1 ratio had recovered to 40%, typical post-tetanic facilitation was seen for up to 1 min after the tetanic challenge, with no obvious undershoot of T1 or T4 below its expected time course (as judged by eye). Later, when the T4/T1 ratio was between 50 and 90%, the post-tetanic facilitation was followed by an undershoot of T4 below its expected time course—the undershoot lasting for up to 3 min. T1 was not affected as obviously as T4. Once T4 had fully recovered, it was not possible to demonstrate post-tetanic facilitation, nor was there any convincing depression of T4 after a tetanic challenge.

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CORRESPONDENCE

RELATIONSHIP BETWEEN EXERCISE-INDUCED MYOLYSIS AND MALIGNANT HYPERTHERMIA

Sir,—We read with interest the article of Hackl and colleagues [1] on the possible relationship between exercise-induced myolysis and malignant hyperthermia. Indeed, "human stress syndrome" should be considered and contracture tests performed when there are important symptoms during exercise.

Our personal experience concerns 11 patients biopsied because of "exercise-induced myolysis", and tested according to the European Malignant Hyperthermia Group procedure [2]. Only one of them, a 2-yr-old boy presenting with hyperthermia and faintness when exposed to exercise, stress and heat, had a positive contracture test to halothane and caffeine. All the others, aged 8–43 yr had clear-cut negative results. Histopathological and histochemical investigation of the muscle did not reveal any precise mechanism to account for the rhabdomyolytic episode.

We are anxious to know if the authors believe that their patient had a familial genetic defect producing the abnormal contracture tests. If so, have they biopsied other members of the family? Furthermore, have they looked for a metabolic myopathy in the two patients?

R. Krivosic-Horber
P. Adnet
H. Reyford
Lille

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2. The European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. *British Journal of Anaesthesia* 1984; **56**: 1267–1270.

Sir,—We appreciate the comments on our paper by Professor Krivosic-Horber and colleagues. In addition to the two reported cases of "exercise-induced myolysis", we examined three more patients presenting with severe muscle pain and pyrexia following physical exercise. In one of these the *in vitro* contracture test was negative, while the halothane test was positive in two (MHEh according to the European Protocol). Consequently, three of five patients had a pathological contracture test [1]. The MH trait was verified by examining the three patients' closest relatives. In all cases, family members turned out to be clear-cut MHS. The subjects reported in the paper to which Krivosic-Horber refers were not examined histopathologically, but one MHEh-proband was examined and showed normal results.

In short, we agree with Krivosic-Horber and colleagues that MH trait is just one possible trigger for exercise-induced symptoms, myolysis, or both. Considering the limited number of cases, the fact that the MH trait was more common among our patients is probably a coincidence.

W. Hackl
M. Winkler
W. Mauritz
Vienna

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MYOTONIAS AND SUSCEPTIBILITY TO MALIGNANT HYPERTHERMIA

Sir,—While the recent paper by Lehmann-Horn and Iaizzo [1] was intriguing, their final sentence is strange: "...non-triggering anaesthesia is indicated." Their results and discussion strongly suggest that, with the exception of a depolarizing drug such as suxamethonium, the volatile agents are safe in myotonia patients. Suxamethonium is, of course, contraindicated because of the benign contracture it is known to produce, but the likelihood of clinical MH is probably not different from that of the general population.

G. A. Gronert
Davis, California

REFERENCE

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Sir,—Thank you for the opportunity to respond to Dr Gronert's comment on our paper. In our work we showed that myotonic conditions are not accompanied by a genetic susceptibility to malignant hyperthermia (MH). On the other hand, we found that not only suxamethonium, but also caffeine and halothane, could cause a temporary increase in the baseline force in the *in vitro* contracture test. This is more likely to be in the form of a tetanic contraction (i.e. associated with electrical activity) than in the form of a contracture. Therefore, the myotonic reaction apparently can be intensified by several substances, in addition to depolarizing substances. That is the reason for our qualifying statement.

We do not know if there are other substances which, although safe with respect to triggering MH in susceptible individuals, intensify the myotonic reaction. The pathological mechanism is certainly different between MH and the myotonias and the periodic paralyses. While the calcium release from the sarcoplasmic reticulum is impaired in malignant hyperthermia [1] (which becomes a concern when the muscle is exposed to trigger substances), the myotonic conditions exhibit an impairment of the sodium channel and possibly also of the chloride channel of the muscle fibre membrane [2, 3].

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29-GAUGE SPINAL NEEDLES

Sir,—Our experience with 29-gauge needles appears to be greater than that of your correspondents [1, 2] to date, and therefore we believe we can add to the debate.

We have used 29-gauge (0.3-mm) needles for spinal anaesthesia for 182 Caesarean sections and 81 other procedures in obstetric patients, and have had one (0.4%) significant post dural puncture headache (PDPH). We define a significant PDPH as a headache severe enough to persuade a woman to accept an extradural blood patch. As we offer a blood patch to any woman whose postoperative wellbeing suffers, and because those who find their mobility restricted rarely refuse, our definition is similar to that of Carrie and Collins [2]. Over the past 5 years in the same population, we have given blood patches to 4% of patients after spinal anaesthesia using 26-gauge (0.45-mm) needles. We suspect that our threshold to patch has decreased because we have given restoration of mobility an increasingly higher priority.

One factor in the development of PDPH which tends to be overlooked is the experience of the anaesthetist. From table I it may be seen that the patch rate of a Senior House Officer is three times that of a consultant. We endeavour to give all our trainees personal instruction in spinal anaesthesia, which includes use of the 29-gauge needle.

Table I. *Incidence of blood patch following spinal anaesthesia by differing grades of staff*

Staff grade	Blood patch (%)
Consultant	2.3
Senior Registrar	2.6
Registrar	3.2
Senior House Officer	7.5

The practical difficulties mentioned by Carrie and Collins [2] translate into a greater failure rate. During 1990 we found that the incidence of failure of spinal anaesthesia with the use of a 29-gauge needle was 6.5%, compared with 4.3% using a 26-gauge needle. The latter figure corresponds to failure rates reported elsewhere [3].

We do not believe that Tuohy-guided spinal anaesthesia is the answer, as we have found that this form of combined spinal–extradural anaesthesia results in a significantly greater number of failures than when each is performed using a separate space [unpublished observation].

Our experience with spinal anaesthesia has brought us to suspect that the 26-gauge needle is too large for obstetric practice, and that the best needle for obstetric practice has not yet been identified. We suggest that contenders should produce an incidence of significant headache which is less than 1%, and a failure rate of less than 4%.

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R. Macdonald
Leeds

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TENSION PNEUMOTHORAX—WRONG TUBE?

Sir,—The case report by Laishley and Aps [1], in addition to demonstrating the benefits of pulse oximetry, also clearly demonstrates one of the defects of the Robertshaw tube.

As the authors observe in the discussion, the patient's right lung could not be re-inflated following upper lobectomy until the bronchial cuff had been deflated. This indicates that the bronchial cuff had herniated across the main carina and was partially obstructing the right main bronchus. In this situation, it is feasible that the cuff would have acted as a ball valve to the right main bronchus, allowing air trapping and the subsequent tension pneumothorax, but it is surprising that no change in compliance was noted.

It is also possible for the herniated cuff completely to obstruct the right main bronchus, resulting in absent ventilation rather than air trapping. This is of little clinical significance if the side of the double-lumen tube used is appropriate to the lung requiring ventilation during surgery. However, it is not uncommon for the left-sided Robertshaw tube to be used in circumstances in which right lung ventilation is required, for example for left thoracotomy for non-pulmonary surgery In this circumstance, herniation of the bronchial cuff may cause obstruction of the ventilated lung. This is detected usually without the aid of a pulse oximeter.

Unless one is aware of the potential for herniation of bronchial cuffs in this design of tube, the problem of sudden inability to ventilate the lung during thoracic surgery may lead to confusion, and is usually resolved only when the bronchial cuff is deflated—often the last resort.

The significance of cuff herniation in the Robertshaw tube may be minimized also by using the correct-sided tube. Attempts to avoid right endobronchial intubation are probably misguided except in the presence of an abnormal anatomical position of the right upper lobe bronchus. This would be detected at bronchoscopy, which should preceed the attempted placement of any endobronchial equipment.

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INAPPROPRIATE HEPARINIZATION WITH A CELL SAVER

Sir,—The use of red blood cell saving systems is becoming more widespread in clinical practice as a result of the obvious advantages of their making possible the transfusion of the patient's own erythrocytes, thus reducing the risk associated with transfusion reactions, infection transmission and reducing the demand for banked blood. These systems are particularly useful where major haemorrhage is anticipated.

Following the recent editorial by Dr Turner [1], I report two consecutive cases in which the patient was unexpectedly heparinized after the use of a "Kardiothor" system. This involves aspiration of freshly-spilled blood via a dedicated suction system to which heparin is added to prevent coagulation during the saving process. The saved cells are then washed, centrifuged and resuspended in saline for subsequent transfusion. This process washes out the heparin, platelet aggregates and plasma proteins, including coagulation factors.

The first patient was a 90-yr-old man who underwent an uneventful emergency repair of a ruptured abdominal aortic aneurysm. A "Biogel" tube graft was used and the patient received 5500 ml from the cell saver, bank blood 6 u and fresh frozen plasma 4 u. At wound closure there was no significant haemorrhage. Postoperative coagulation screen revealed a prothrombin time of 27/14 s, activated partial thromboplastin time (APTT) > 300 s and thrombin time (TT) > 100 s. Reptilase time was performed to ascertain that the anticoagulant was indeed heparin (reptilase is a venom which reactivates the coagulation system in the presence of heparin). This was normal.

A sample from the last bag of cell saved blood was added to normal plasma and found to inhibit coagulation. Protamine sulphate 100 mg was administered to antagonize heparin, with immediate improvement in coagulation (PT 24/14 s; APTT 51/34 s). However, the patient continued to bleed, requiring transfusion of packed cells, fresh frozen plasma, cryoprecipitate and platelets. Repeat laparotomy was performed, but no specific bleeding points were noted and the patient's condition eventually stabilized. Subsequent protamine titration of the sample of cell saved blood revealed heparin at a concentration of 2 u ml^{-1}, implying therefore a total dose in excess of 10000 u.

The second patient was a 60-yr-old man who had an elective aorto-bifemoral bypass graft, right renal artery revascularization and left nephrectomy. Because of the problem with the previous patient, a representative from the cell saver company was present, together with a senior medical laboratory technician who performed immediate tests on all cell saved blood to be transfused, including coagulation screens on the patient. Similar problems again were encountered, although not to the same extent. Protamine titrations revealed heparin concentrations of 0.75 u ml^{-1} in some resuspended samples.

The problem with the system related to the angulation of the light sensor apparatus, the function of which is to detect when the erythrocytes have been separated from the supernatant containing the added heparin and other blood constituents. This may be disturbed during transit and may occur with any system if it has been transported.

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UNCERTAINTIES ABOUT THE VENTILATORY RESPONSE TO HYPOXAEMIA

Sir,—The recent review entitled "Effects of Anaesthesia on Respiration" by Dr J. F. Nunn [1] is especially valuable in that it addresses uncertainties about knowledge in this field. A section of the review implies uncertainty about our knowledge of the ventilatory response to hypoxaemia in anaesthetized humans. Studies of this response are said to have been limited. Unfortunately, the characterization of these studies is mistaken. I believe it important to correct the misrepresentations that were made inadvertently and to clarify the basis for uncertainty in this area.

The review states that the number of subjects who took part in these studies was limited. However, the total number of individual subjects in this series of studies was considerable, namely 121 [2–11]. The review states that the subjects of the study comprised only the investigators themselves. The fact is that only six of the 121 subjects were investigators; 115 subjects were not. Only one of the investigators participated in more than one project.

The review also indicates that the full extent of individual variation in the effect of anaesthetics on this response was not explored. However, some reasonable insights about individual variation were obtained. For example, the most important observation—the abolition or near abolition of the response to hypoxaemia by light anaesthetic doses of halothane, isoflurane or enflurane—was seen consistently in 62 individual subjects. Although most subjects were tested during exposure to only one of the three halogenated agents, each agent produced virtually the same mean effect and the variation amongst individual subjects was limited [2, 3, 6, 7, 10, 11]. Furthermore, additional factors that may have altered or varied the effect (an increased $P\text{CO}_2$, added H^+ activity, or the presence of surgical stimulation) were found to modify neither the effect nor its variation in important ways [2, 3, 7, 11]. Another observation—the substantive reduction of the hypoxaemic response produced by the subanaesthetic dose of the halogenated agents—was explored in an equally extensive fashion and in a similarly large group of subjects [2, 5, 6, 9–11]. Accordingly, it would seem that this research has yielded a substantial amount of information about the variation of this particular anaesthetic effect.

It is important that comprehensive reviews identify uncertainties in knowledge. It is also important that they define accurately the basis for the uncertainties. In the case of the ventilatory response to hypoxaemia during anaesthesia, uncertainties certainly exist, but they would seem to arise not so much from the type and number of subjects studied previously as from the fact that all reported studies have been undertaken by a single group—our group at the University of Western Ontario. To my knowledge, none of the findings of these studies has been corroborated or refuted by other investigators. Although there are obvious ethical constraints in studying physiological responses to hypoxaemia in anaesthetized humans (as alluded to in Dr Nunn's review) these constraints need not preclude useful research, as was pointed out elsewhere [12].

I do hope that other investigators recognize the need for further study of the ventilatory response to hypoxaemia during and after anaesthesia in humans and that they appreciate the feasibility of investigating this response in an ethical manner. Even though the available observations are much more extensive than acknowledge by the review, we do need to advance present knowledge to more certain grounds.

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Sir,—My friend Dr Knill has already pointed out to me that I have misrepresented his studies in my review [1]. I can do no more than present my unreserved and public apology for mistakenly relying on my memory of his classic papers, which I had read some years ago. He had indeed studied adequate numbers of patients, and reached his conclusions beyond any reasonable doubt.

Nevertheless, as Dr Knill himself states, there has been a reluctance for these crucially important findings to be confirmed in other centres. No doubt one factor has been the ethical constraint inherent in reducing the arterial Po_2 of anaesthetized patients to 6 kPa (45 mm Hg) for experimental purposes. I am not saying that such a study is "unethical", but rather that one should not embark upon such work without the most careful consideration of the risk:benefit ratio, the nature of the informed consent and minimizing the number of patients required to establish the finding. I know that Dr Knill and his Ethics Committee did give these matters the most careful consideration.

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REGIONAL ANAESTHESIA REQUIRES ATTENTION TO DETAIL

Sir,—Two papers [1, 2] published in the March 1991 issue of *British Journal of Anaesthesia* are clear reminders of the importance of attention to detail when performing regional anaesthetic techniques, but both require some further comment.

Ievins claims that "standard" methods of identifying L4 are not particularly accurate, but I would suggest that the method he used—"dropping an imaginary vertical line"—was not the standard practice of experienced practitioners. His subjects were cadavers, and presumably they were in an approximately anatomical position. I would suggest that the construction of Tuffier's line in a patient with hips and spinal column flexed maximally is "standard" practice. It is what is advocated by all the texts on my shelf. As a regular user of thoracic extradural block, I must also take great issue with the bald statement that the spinal cord is at "considerably more risk of damage" when needles are inserted at higher levels. Like all practical procedures in medicine, "it is not what you do, it is the way that you do it"!

Perhaps the same message is relevant to the description by Lee and Parry of a case of meningitis after spinal anaesthesia for Caesarean section. Although other possibilities must not be lost sight of, I would agree with their assessment that this was probably a bacterial infection and it seems very likely that the infection was introduced at the time of lumbar puncture. I cannot agree that this was "despite meticulous aseptic techniques" It is clear that whoever gave the anaesthetic did not wear a surgical facemask. I believe that the anaesthetist should always wear such a mask when performing a central nerve block. During both preparation and needle insertion, the anterior nares and mouth are relatively close to, and usually immediately above, the sterile field. The arguments put forward in defence of the practice of not wearing a mask are based primarily on studies of ward practice and may not be relevant. The effect of contamination, especially with particulate matter, may be more significant because any bacteria that do gain access are placed in an ideal culture medium, which is relatively deficient in host defence mechanisms. Bacteria can, as this case shows, multiply very rapidly in that situation. In my opinion, a mask should be worn.

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Sir,—Thank you for the opportunity of replying. I agree that all the standard texts advocate drawing Tuffier's line on the subject's back. However, it is my experience, gained in several units and from watching many practitioners, that extradurals are frequently sited by lying the patient on the side, palpating the upper iliac crest and running the hand down to the vertebral column, rather than palpating both iliac crests and joining them. It is precisely this need for meticulous attention to detail that I was trying to convey.

Regarding the comments concerning the risk to the spinal cord. I did not intend to imply that thoracic extradural blocks are dangerous. Rather, I was trying to draw attention to the fact that intradural needles, if sited higher than anticipated, might put at risk a cord terminating lower than normal.

F. A. IEVINS
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FAILED TRACHEAL INTUBATION

Sir,—Dr King and Professor Adams correctly state that the Laryngeal Mask Airway (LMA) has been used successfully after failed intubation at Caesarean section [1, 2]. However, if a decision is made to insert the LMA in the obstetric patient we would question the timing of insertion, which they state should be after spontaneous ventilation has resumed.

We would suggest that when failure to intubate has been acknowledged, and in the unfortunate situation that the patient's lungs are difficult or impossible to ventilate manually, the LMA should be inserted at that time rather than wait until the gravity of the situation has rectified itself by resumption of spontaneous ventilation. Alternatively, in the hopefully rare situation when it is felt that surgery must proceed in the patient in whom it is impossible to intubate the trachea, but who has a reasonably clear airway, it might be prudent to pass the LMA in the still paralysed patient before spontaneous ventilation has resumed, as insertion of the LMA might be technically more straightforward.

The correct use of the LMA provides a safer means of maintaining ventilation before last-ditch attempts at cricothyroid puncture or tracheotomy.

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Sir,—Thank you for the opportunity to reply to this letter. We wish to draw attention to recent correspondence by Freeman and Baxendale, in which the possible dangers of insertion of the Brain laryngeal mask airway after a failed obstetric intubation are described clearly [1].

In our opinion, should ventilation with a face mask be easy after failed intubation in an obstetric patient, insertion of the Brain laryngeal mask airway at this stage would, at the very least, be meddlesome. This is the most critical stage, when one awaits return of spontaneous ventilation while maintaining oxygenation and preventing aspiration. In the event of inability to ventilate the patient's lungs with a face mask, insertion of the Brain laryngeal mask airway may well be appropriate. However, insertion of the laryngeal airway may not be straightforward under these circumstances and, as with tracheal intubation, prolonged attempts at insertion should be avoided. Cricothyroid puncture performed at the correct time with appropriate equipment will be life saving.

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TRACHEAL INTUBATION WITH THE PATIENT IN A SITTING POSITION

Sir,—Occasionally, the anaesthetist is required to provide general anaesthesia for a patient with a difficult airway and a full stomach. In some instances, these patients may have concurrent cardiovascular or cerebrovascular disease or increased intracranial pressure, and would benefit from a smooth intubation technique that prevents wide variations in cardiovascular variables. With adequate topical and regional anaesthesia of the airway, the cardiovascular responses to laryngoscopy and intubation may be minimized; however, the risk of silent aspiration is greatly increased.

Before the availability of the fibreoptic laryngoscope, the preferred technique was an awake intubation. Topical anaesthesia and sedation were kept to a minimum in an attempt to maintain the protective laryngeal reflexes and decrease the likelihood of gastric aspiration. With the advent of the fibreoptic laryngoscope, management of the difficult airway was made sigificantly easier, but the fundamental conflict remains unchanged. One could have the patient *supine* and use continuous cricoid pressure, but this would have to be maintained for 5–10 min while anaesthesia of the airway developed gradually. However, as anaesthetists may have problems with its safe and efficient application [1, 2], and given the possible occurrence of carotid body stimulation [3] and the potential for oesophageal rupture, cricoid pressure should not be thought of as completely efficient or safe. Cricoid pressure may make the insertion of the fibreoptic scope followed by the tracheal tube difficult [4], and may be adandoned momentarily, with possible disastrous consequences. We recommend an alternative approach based on the following anatomical and physiological observations.

Intragastric pressures measured in normal fasting adult patients may reach 30 cm H_2O [3, 5]. In most adults, the distance between the lower oesophageal sphincter (LOS) and the upper oesophageal sphincter exceeds 25 cm. Thus, even if the LOS provides limited resistance to the efflux of gastric contents, it is highly unlikely that the normal intragastric pressure responsible for passive regurgitation would be sufficient to propel gastric contents into the oropharynx in a patient sitting fully upright or standing. Based on the above, the anaesthetic management to secure the airway should begin with the appropriate pretreatment to decrease gastric volume and acidity while increasing LOS tone [5–11]. Thereafter, the patient should be placed in a fully upright sitting position but with hip flexion minimized. Adequate anaesthesia of the airway then should be achieved with a combination of topical and regional anaesthetic techniques: 10% lignocaine sprayed into the oropharynx (six to 10 puffs, 10 mg per puff), 2% lignocaine 2 ml injected through the cricothyroid membrane to provide intratracheal anaesthesia, and superior laryngeal nerve block 5–10 min before instrumentation. Finally, a standard oral fibreoptic intubation technique should be used to secure the airway.

Although there is no clinical trial to support our contentions, we have experience to indicate that this technique may maximize patient safety while providing minimum stress and discomfort to both patient and anaesthetist. We wonder if others have any comments on this management.

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ANALGESIA WITH SUBHYPNOTIC DOSES OF THIOPENTONE AND PROPOFOL

Sir,—The study by Anker-Møller and colleagues documents well the effects of subhypnotic doses of thiopentone and propofol on experimentally induced acute pain [1]. In a pilot study with thermally induced first pain [2], we compared the effects of steady state infusions of propofol 1 and 5 mg kg^{-1} h^{-1}, thiopentone 2.5 and 12.5 mg kg^{-1} h^{-1} and etomidate 0.1 and 0.5 mg kg^{-1} h^{-1}. We also found that propofol in the greater dose demonstrated analgesic effects, but in the smaller dose was associated with hyperalgesia. Moreover, thiopentone was associated with hyperalgesia at all doses. Etomidate showed neither analgesic nor hyperalgic effects. Our results are in accordance with previous studies [3, 4].

Several questions arise in trying to explain the discrepancy with the results of Anker-Møller. First, the effect of cortical depression (sedation) on pain-evoked potentials is not discussed. Were the degrees of sedation achieved constant and comparable, as long latency potentials are notoriously susceptible to pharmacological and physiological influences [5]? Second, electrophysiological studies under non-steady state conditions are difficult to interpret; the balance between neuronal inhibition and excitation is different between bolus and steady state conditions. Third, does laser stimulation really produce a pure "first pain", as the rate of change in skin temperature is very high, and may be unphysiological and associated with chemical nociceptive activation?

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A. Borgeat
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Sir,—Previously, we have used both laser and thermode stimuli and concluded that the distinct, first pain perception, evoked by brief argon laser stimuli differs in quality and intensity from the pain elicited by a slowly heating thermode. We have compared the effect of local anaesthetics on both laser and thermode thresholds and found a different effect on the two thresholds [1]. This discrepancy may be explained by activation of different nerve fibre populations ($A\delta$- and C-fibres); a different number of receptors activated (spatial summation); a different duration of receptor activation (temporal summation); and the fact that lasers do not cause concurrent activation of mechanosensitive afferents as a touching thermode. Furthermore, brief cutaneous laser stimuli cause a very fast increase in intracutaneous temperature which is known to generate high frequency bursts of activity from nociceptors. From a physiological point of view, lasers seem to be adequate for cutaneous pain stimulation. Traditional pinpricks also cause bursts of neuronal activity, but this stimulus cannot be controlled or quantified. Pain perceptions evoked by laser and pinprick stimuli are similar in quality, but different from pain elicited by thermodes. It is, therefore, not surprising that different results are obtained by different stimulation techniques.

The characteristics of the long latency pain-evoked potential are similar to long latency (vertex) potentials evoked by other sensory modalities. These vertex potentials are sensitive to changes in vigilance and hence the degree of sedation. The modulation of pain-evoked potentials by thiopentone or propofol therefore, may be caused by both an anaesthetic and a sedative effect, and the contribution of the individual factors could not be separated. It can be argued that an overall measure which is sensitive to both anaesthetic and sedative effects may be a good correlate with clinical practice, in which pain alleviation often is obtained by a combination of both factors. The purpose of the present study was to elucidate if single subhypnotic doses of thiopentone or propofol caused hyper- or hypoalgesia to acute pain. If hyperalgesia was obtained, we would expect to see an increase in the size of the potential [2].

The latency of the laser-evoked potential is not affected by sedation [3] and therefore we have proposed this variable for quantification of peripheral and central conduction properties along the pain pathway [4, 5]. As this information cannot be obtained by threshold determinations, we always use both evoked potentials and thresholds for assessment of anaesthetic efficacies.

The use of laser-evoked potentials and pain thresholds in anaesthesia is a fairly new approach, and investigation of how these measures respond to various interventions along the pain pathway enables us to determine their applicability and validity for testing and comparing anaesthetic procedures and substances.

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INCREMENTAL SPINAL ANAESTHESIA AND CAESAREAN SECTION—RELEVANCE TO THE TEST DOSE FOR EXTRADURAL ANALGESIA

Sir,—It is possible to administer an otherwise catastrophic dose of bupivacaine into the subarachnoid space of a pregnant women at term without ill effect, provided she is kept static. Kestin and colleagues demonstrated this in their study of incremental spinal anaesthesia for Caesarean section [1]: one of their mothers required bupivacaine 37 mg intrathecally to achieve effective anaesthesia. In the next issue of the Journal, Randall and colleagues, in their study on spinal anaesthesia for Caesarean section obtained a large number of high blocks with bupivacaine 12.5 mg [2]. Their mothers were subjected to a change of posture after a single spinal injection: the mothers were moved from full left lateral through supine to 15° right tilt. This manoeuvre produces a brief period of inferior vena caval (IVC) compression sufficient to cause acute engorgement of the extradural veins, and a cephalad surge of CSF results. Whatever the extent of this surge, it is enough to add a significant impetus to the spread of administered drugs intrathecally. It has been shown that IVC compression is essential to produce good filling of the extradural veins during lumbar extradural venography [3].

All the evidence [1–3] continues to support Russell's hypothesis that sudden diversion of blood into the vertebral venous system decreases the space available for CSF at the caudal end of the subarachnoid space [4]. This dynamic effect of IVC compression is in addition to any influence on drug distribution of the reduced lumbosacral CSF volume caused by sustained congestion of the adjacent extradural veins. In this regard, it should be noted that IVC compression is not necessarily relieved adequately by tilt in some individuals.

The above observations suggest that the test dose for accidental intrathecal placement of the extradural catheter should be performed in two stages. The first stage consists of the test dose being administered with the mother in the full left lateral position, when the extradural veins are relatively collapsed. The second stage requires that the mother is moved into the supine position for about 30 s before being tilted by insertion of the pelvic wedge. Only then may the absence of symptoms and signs of inadvertent intrathecal injection be taken to signify a likely correct placement in the extradural space.

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Sir,—As Dr Tunstall states, moving pregnant mothers after an intrathecal injection of local anaesthetics does have major effects on the extent of the block, and has implications for test doses through extradural catheters.

If a test dose of plain 0.5 % bupivacaine is given through an extradural catheter *after* the patient has been moved supine with a left tilt, a spinal block may not be apparent until a considerable dose of bupivacaine has been given. The patient in our study who required a total of 7.4 ml of 0.5 % plain bupivacaine had a spinal block to only S1 after 2.5 ml. This dose would be used commonly as a test dose through an extradural catheter, and this degree of block would easily be missed with cursory testing.

If a test dose of plain 0.5 % bupivacaine is given with the mother on her side and then turned supine, as Dr Tunstall suggests, this would mimic the usual clinical practice of spinal anaesthesia. Clinical experience suggests that a recognizable spinal block should be obvious after 12.5 mg of 0.5 % plain bupivacaine. However, it cannot be concluded from either of the two studies cited by Dr Tunstall that a spinal block would *always* be recognizable. Unfortunately, this is what is required of an ideal test dose—that it never fails.

Dr Tunstall's suggestion should improve the sensitivity of test doses, but constant vigilance and awareness of the large variability between patients remain the most important safeguards.

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British Journal of Anaesthesia 1991: 67, 229–230

BOOK REVIEWS

Advances in Anesthesia, Vol. 7. Edited by R K. Stoelting, P. G. Barash and T. J. Gallagher. Published by Year Book Medical Publishers, Chicago. Pp. 379; indexed; illustrated. Price £45.00.

The seventh volume of *Advances in Anesthesia* contains 12 chapters written almost exclusively by American anaesthetists. The majority hold university posts and there is a good mixture of junior and senior authors. The topics covered in the chapters include the predictable, such as AIDS and its implication for the anaesthetist, and the pulmonary artery catheter: do complications outweigh the advantages?, to the less common, such as anaesthesia simulators and alternative routes of drug administration. The length of the articles varies considerably from as few as 15 to as many as 56 pages. This unevenness is reflected also in the number of references cited: Ruth Maxson quotes 241 references in a thorough review of monitoring and antagonism of neuromuscular block; some of the shorter chapters read as if they are extended lists taken from lecture material, so that there is little critical discussion of the recent literature.

This difference in the depth of the reviews highlights the important question of exactly for whom this book is intended. The shorter chapters serve examination candidates admirably, but lack sufficient detail for research workers. Conversely, the longer chapters are an excellent source of references, but are unnecessarily complex for most examination candidates. The absence of a Preface does not help to answer this question.

The book is produced to a high standard with few errors, but is competing with many similar volumes. It would be improved if the Editors standardized the length and complexity of the chapters to ensure a more consistent work. In an area of the anaesthetic literature which already appears to have too many books of this type, I rate it as about average.

G. M. Hall

Epidural and Spinal Blockade in Obstetrics. Edited by F. Reynolds. Published by Harcourt Brace Jovanovich Ltd, Sidcup. Pp. 249; indexed; illustrated. Price £17.50.

This textbook is an extension of a concept developed by Andrew Doughty, who edited two books following Obstetric Anaesthetic Association (OAA) symposia in 1971 and 1979. In 1989, the OAA held a symposium on extradural and spinal block in obstetrics and this provided the basis for this book, which is presented as an update of recent advances in obstetric analgesia and anaesthesia covering the 10-year period 1979–1989.

The editor has divided the book into six major sections, in each of which the authors discuss the points of greatest advance or controversy in that area. The sections are: Introduction (Anatomy of epidural region; indications/contraindications); Management of Labour (Test doses; the second stage); Complications (Risks and how to avoid them); Caesarian Section (Regional versus general anaesthesia); Spinal Opioids; The Recipient.

Unlike many publications following symposia, this is not a transcript of the spoken word. Each author has written his or her chapter specifically for the book with the result that, in spite of a multiplicity of authors, the book is cohesive and readable.

The discussion at the end of each chapter, based on the discussion that took place at the symposium, adds depth to the work and brings out the controversial aspects of many of the topics.

The editor states that the book is aimed at trainee anaesthetists, midwives and obstetricians. However, I feel that it will prove to be of greater value to established obstetric anaesthetists and to experienced trainee anaesthetists, because it leaves many of the fundamental areas uncovered and assumes that the reader already has a considerable basic knowledge of extradurals and spinals in obstetrics. This would possibly confuse the "learner" anaesthetist or obstetrician, and be of limited value to most midwives, all of whom may be looking for more comprehensive and uncontroversial information.

Nonetheless, the book is an informative and well referenced update on extradural and spinal anaesthesia in obstetrics. Although not by any means comprehensive, it deals well with the chosen topics which are pertinent to recent advances. It upholds the tradition of the previous updates of 1971 and 1979 and the pace of change allows room for this exercise to be repeated every decade. It is a book that I would thoroughly recommend to all obstetric anaesthetists and I should like to see a copy in every medical library and delivery suite.

A. May

Anaesthesia for Ambulatory Surgery, 2nd Edn. Edited by B. V. Wetchler. Published by J. B. Lipincott Company, Philadelphia. Pp. 690; indexed; illustrated. Price £69.50.

The first use of day-case ambulatory surgery was in 1919 at the Royal Hospital for Sick Children in Glasgow. Recently, there has been a resurgence of interest in this area, initially in the U.S.A. In the U.K., practice has followed this lead and the recent formation of the Daycase Anaesthesia Society indicates the extent of this enthusiasm. In this book, containing 10 chapters written by 21 transatlantic contributors, the editor has succeeded in conveying the enthusiasm for the subject in the U.S.A.

"What are the challenges?" asks the preface. The succeeding sentence outlines the book's approach in stating that information is provided to meet this challenge; however, its nature may not be so clearly apparent. Undoubtedly, there is a great deal of information in these chapters, but much is not confined to day-case anaesthesia and surgery alone. One chapter has almost 500 references!

Not surprisingly, the book is most relevant to U.S. practice: citing "JCAHO" guidelines, referring to freestanding surgery facilities, and containing chapters on marketing, selection and legal implications. A very good chapter on the paediatric patient omits mention of the use of "EMLA" and the reader should be aware, for example, of the differing recommendations for prevention of bacterial endocarditis in the U.K. Some 10% of the book is occupied by examples of forms and policies, preoperative instructions and information leaflets from various centres of surgery. Some may enjoy the format of certain chapters where a case history is followed by discussion; but this may not be the most balanced method to convey information on this subject. Chapter 7, on problem solving in the postanaesthesia care unit, is more closely focused, providing useful information and references. The author (also the editor) makes sensible suggestions, for example in the differentiation between "home ready" and "street fit" in respect of criteria for discharge. This chapter could stand alone and provide worthwhile reading.

There is much repetition of material. Those seeking answers to specific problems may have difficulty in finding specific answers. The candidate for the Part 3 examination may soon discard this in search of a more succinct text. The consultant wishing to enhance his own techniques and practice may find some useful information in places. For the anaesthetist wishing to embark upon the organization of day-case anaesthesia there is undoubted value, but much adaptation is necessary for this to apply to either existing or proposed U.K. practice.

D. Fell

The Lung—Scientific Foundations. Edited by R. G. Crystal, J. B. West, P. J. Barnes, N. S. Cherniack and E. R. Weibal. Published by Raven Press, New York. Pp. 2224; indexed; illustrated. Price $270.00.

This massive treatise is presented in two volumes encompassing more than 2300 pages (including indexes) and it clearly represents a triumph of organization and editing.

Volume 1 is composed of four sections entitled General Cell Biologic Processes in the Lung, Major Components; Integrated Morphology; Growth and Form; and Integrated Physiology and Pathophysiology. Each of these sections is further sub-divided into chapters varying in number between 8 and 42.

Volume 2 is composed of major sections entitled Pulmonary Gas Exchange, The Fetal, Perinatal, Post-natal and Aging Lung; Lung Injury, Defence, and Repair; and Special Environments and Interventions.

Those sections of most interest, for example Gas Exchange and Oxygen and CO_2 Transport and Pulmonary Mechanics, will be familiar to anaesthetists. The material in these sections is described equally as well elsewhere in texts which are more useful to anaesthetists.

This compendium is designed to cover the whole field of the scientific foundations of the lung in health and disease and the editors believe that the material contained is as contemporary as possible. Indeed, they state that "while a large compendium like this cannot compete with a journal for publication promptness, this book is not far behind". This reflects a triumph of hope over wisdom and experience; for example, postoperative pulmonary function is described in only one half-page of text and the most recent reference is 1986, whilst the majority antedate 1973.

This book clearly has a role only in large institutional libraries and is not appropriate for anaesthetic departmental libraries.

G. Smith

Basic Physics and Measurement in Anaesthesia, 3rd Edn. Edited by G. D. Parbrook, P. D. Davis and E. O. Parbrook. Published (1990) by Butterworth-Heinemann. Pp. 344; indexed; illustrated. Price £25.

This book was conceived originally as a series of tape slide lectures which proved to be so popular that the authors were led to write a book, first published in 1982, with a content similar, but not identical to, that of the audiovisual series.

This third edition differs from the second published in 1985 largely by inclusion of new techniques of measurement, such as pulse oximetry, and expansion of sections describing techniques which have grown in popularity in the past few years, such as capnography. An opportunity has been taken also to effect changes consequent upon revised British and international standards.

Although there are now several books available on physics and clinical measurement in anaesthesia, there is little doubt that for those with a limited understanding of this subject, Parbrook, Davis and Parbrook provide the best text available. This book describes complex concepts and equipment in simple, easily understood terms and is illustrated beautifully with simple line diagrams. It is recommended thoroughly to all candidates for higher examinations in anaesthesia and for all senior staff who wish to refresh their memories of physical principles applicable to anaesthesia.

G. Smith

Gas Monitoring and Pulse Oximetry. By J. S. Gravenstein. Published by Butterworth Scientific Ltd, Guildford. Pp 148; indexed; illustrated. Price £18.00.

This is a single author publication and its stated purpose is to describe the theoretical background of the administration of anaesthesia and ventilation. It is a small book and approximately 50% is given to illustrations.

Rather than describing his chosen topic comprehensively and in a logical fashion, the author has chosen to examine selected areas only. Some are described well but, unfortunately, most are dealt with rather superficially. ("The book is kept brief because it was written for the busy clinician.") The reader is left with the impression that the texts of 16 lectures have been combined together under the vague title of "Gas Monitoring and Pulse Oximetry".

It is difficult to recommend this book, as all of its contents can be found in any of the standard anaesthetic texts. Furthermore, it cannot be described as a good and comprehensive specialized textbook because of the illogical choice of wide ranging subject matter.

D. J. Rowbotham

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

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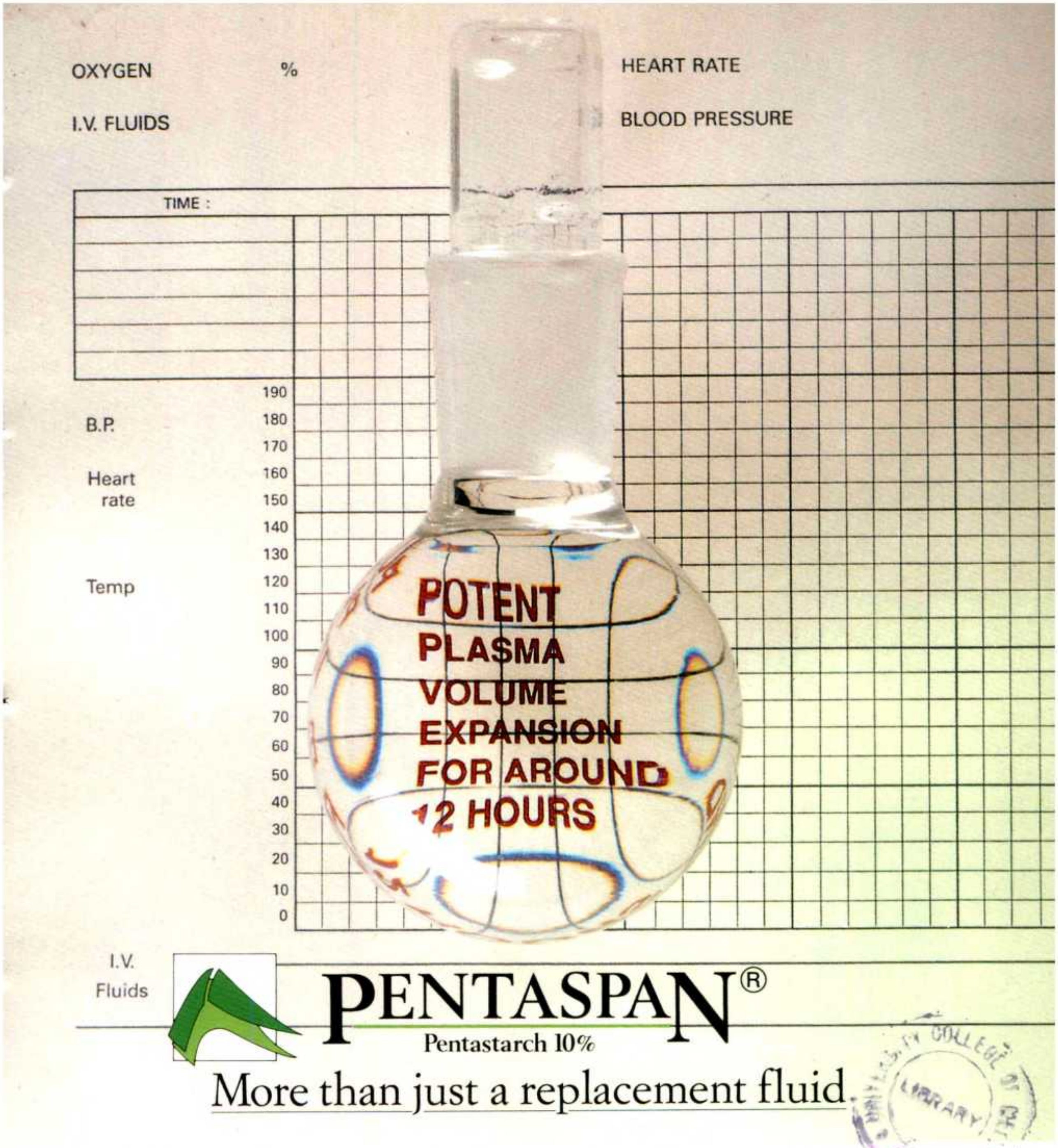

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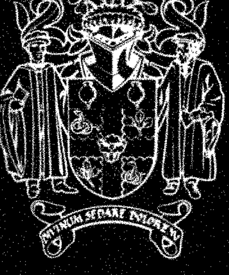

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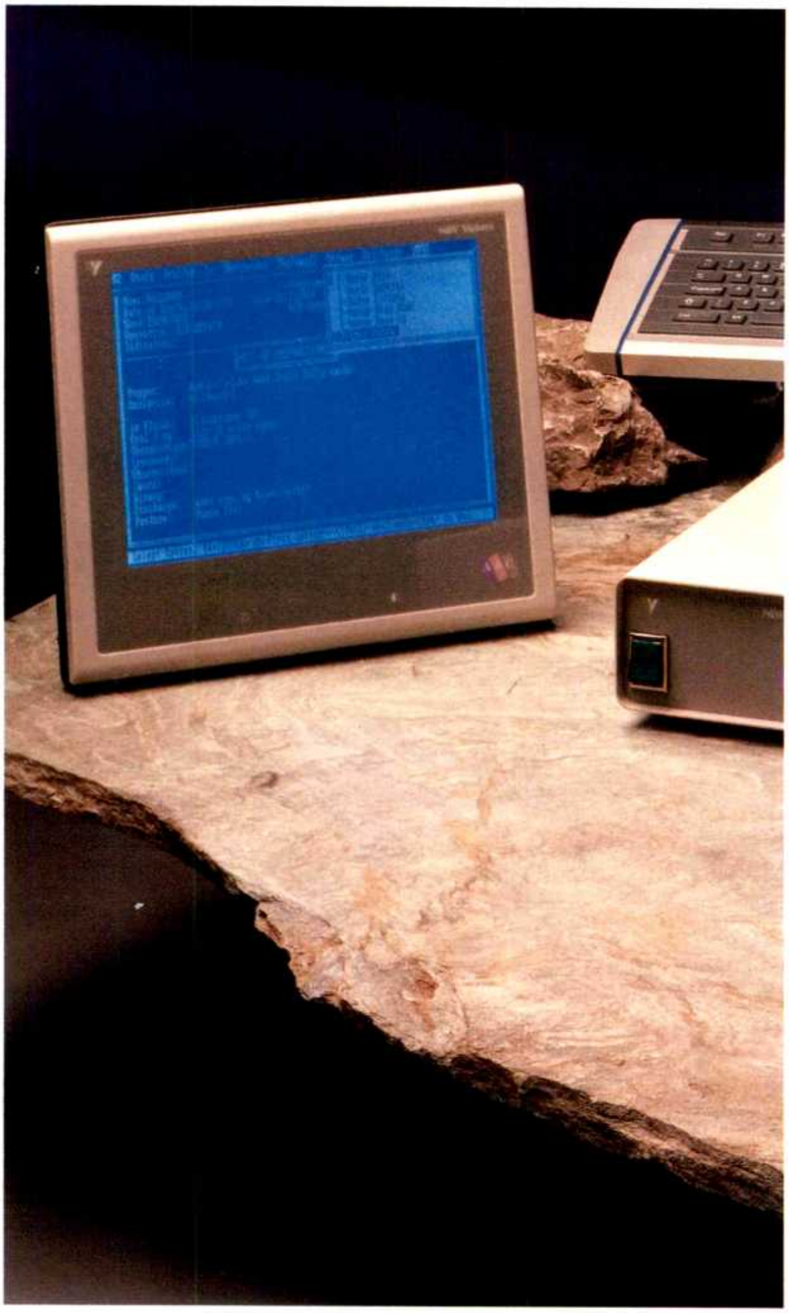

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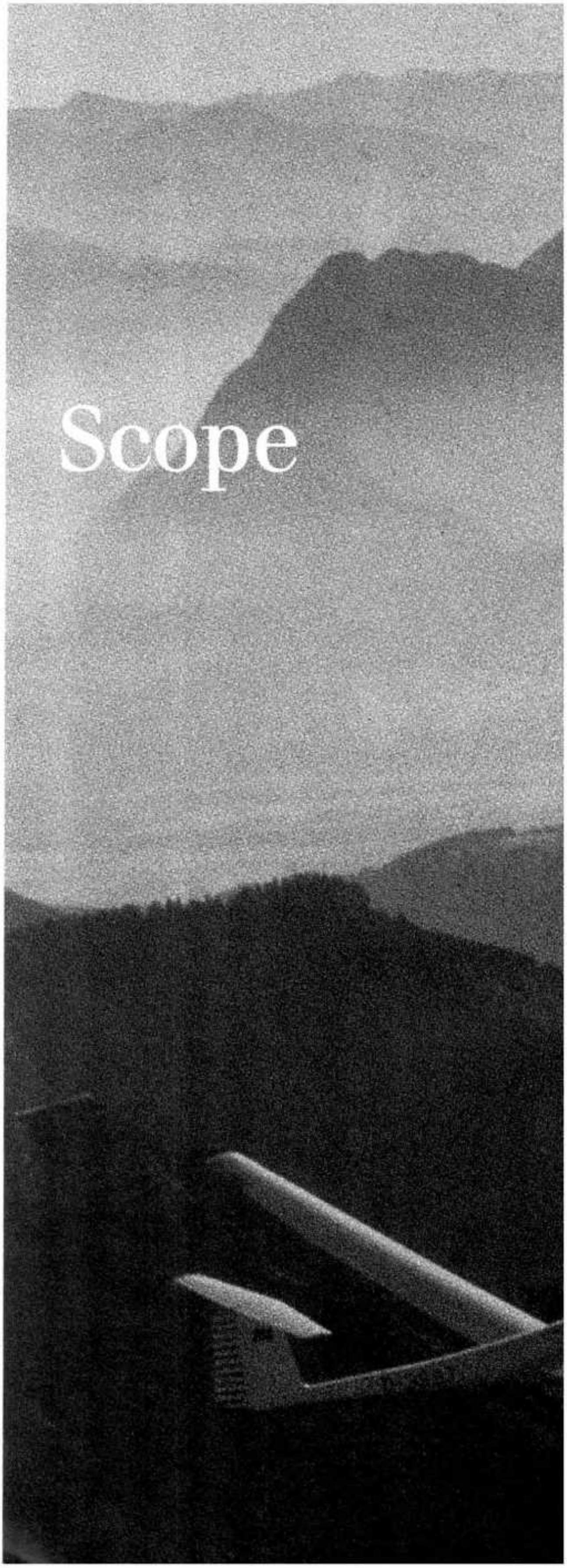

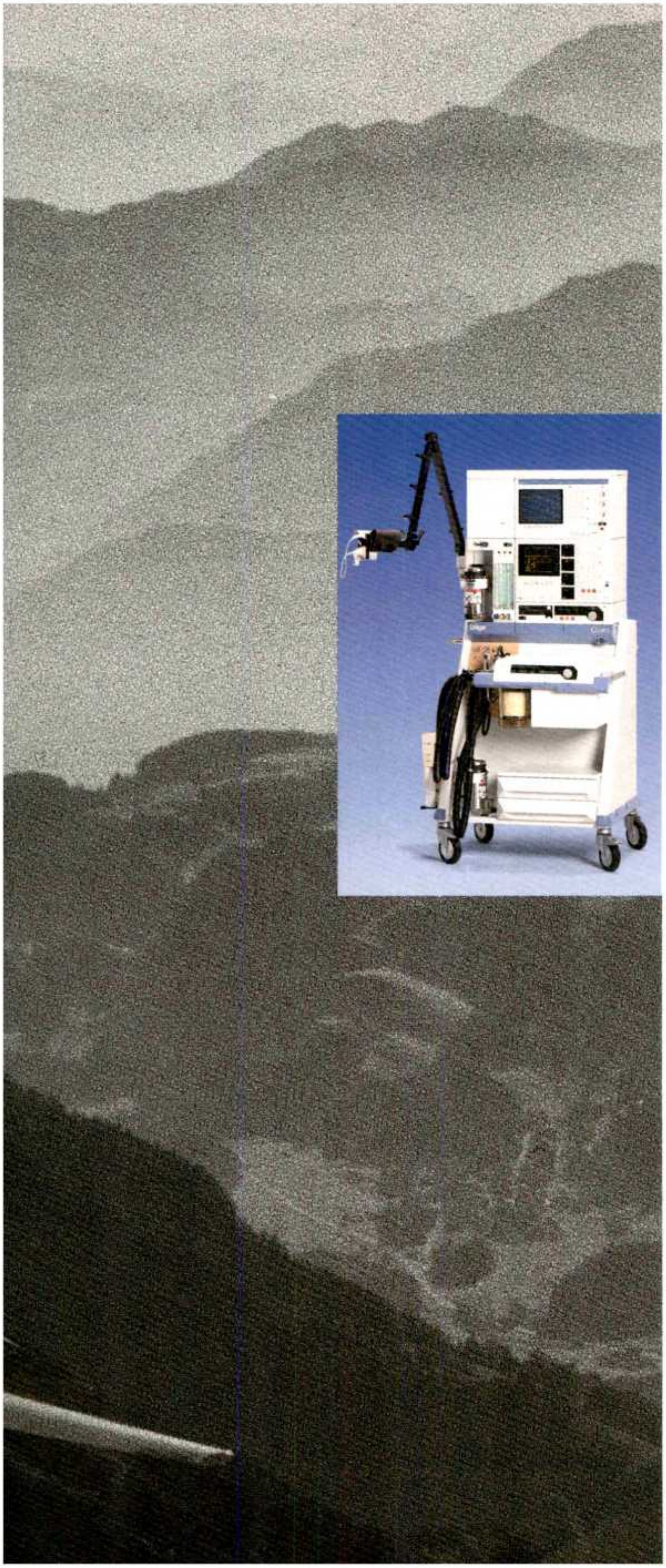

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For further information, please contact:

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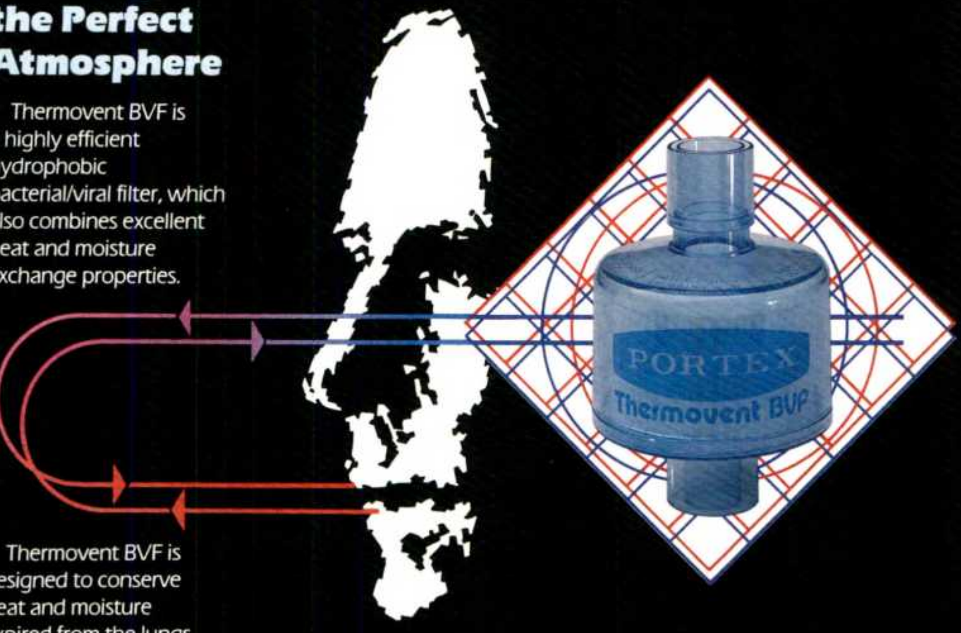

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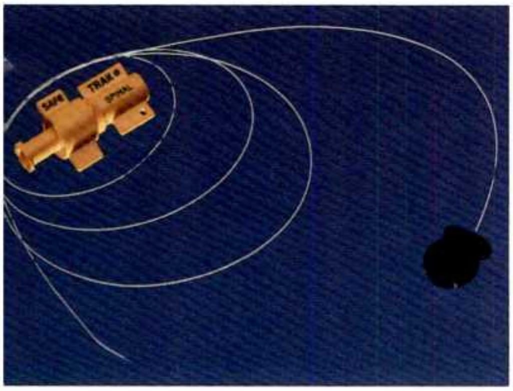

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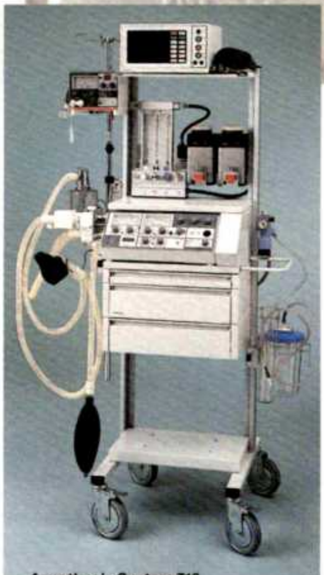

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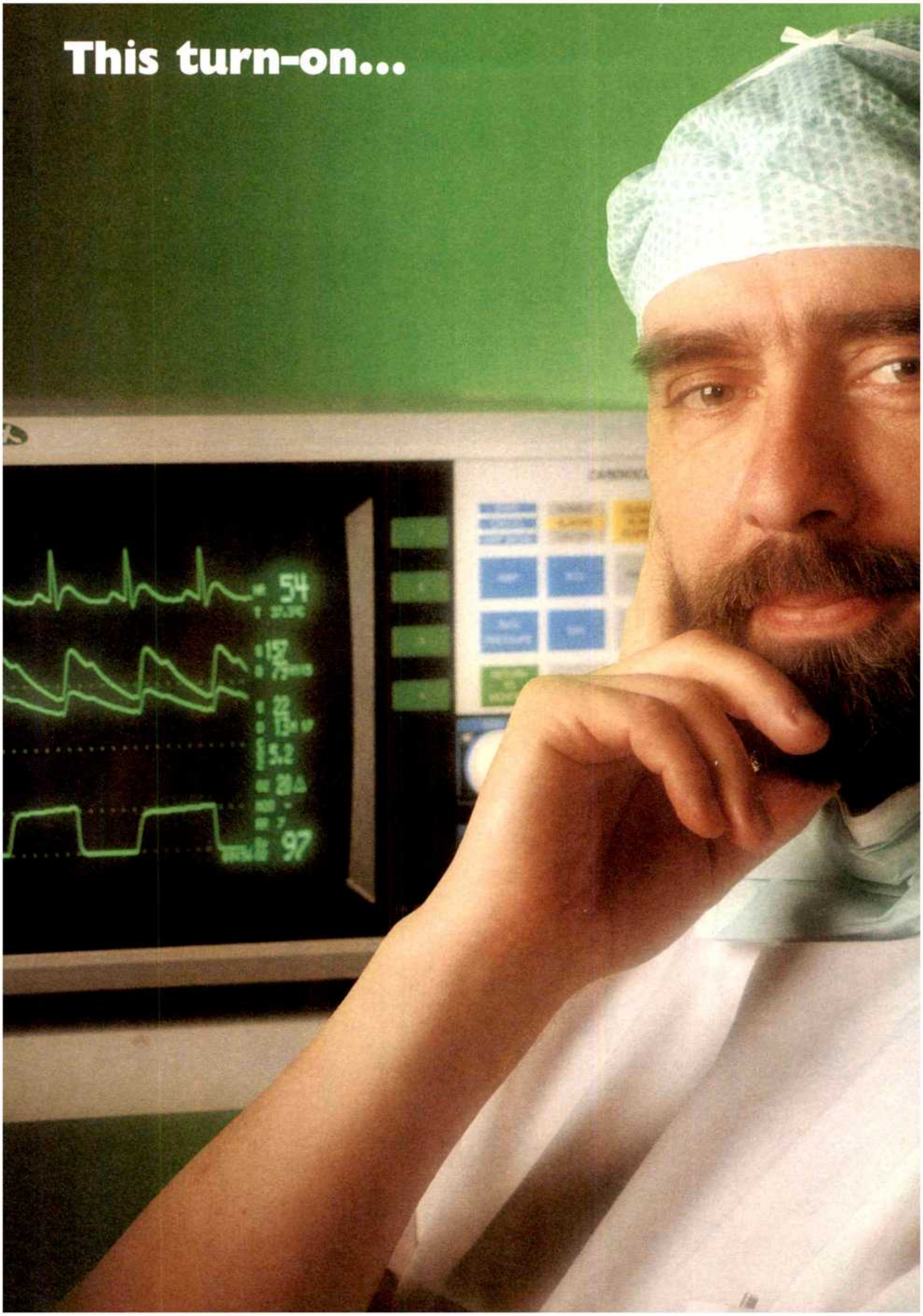
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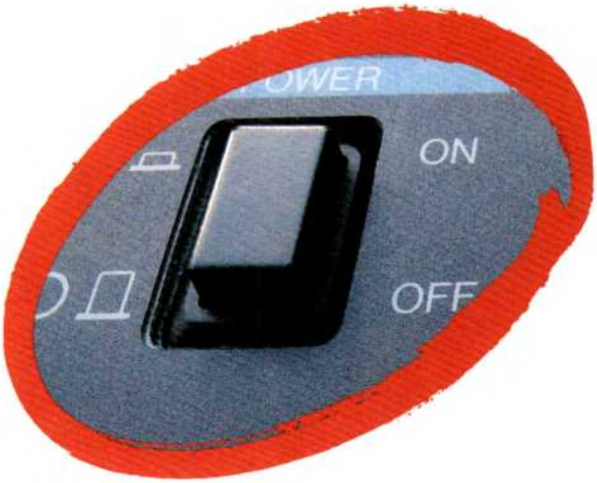

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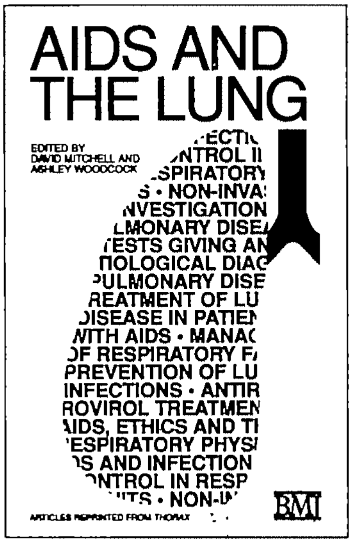
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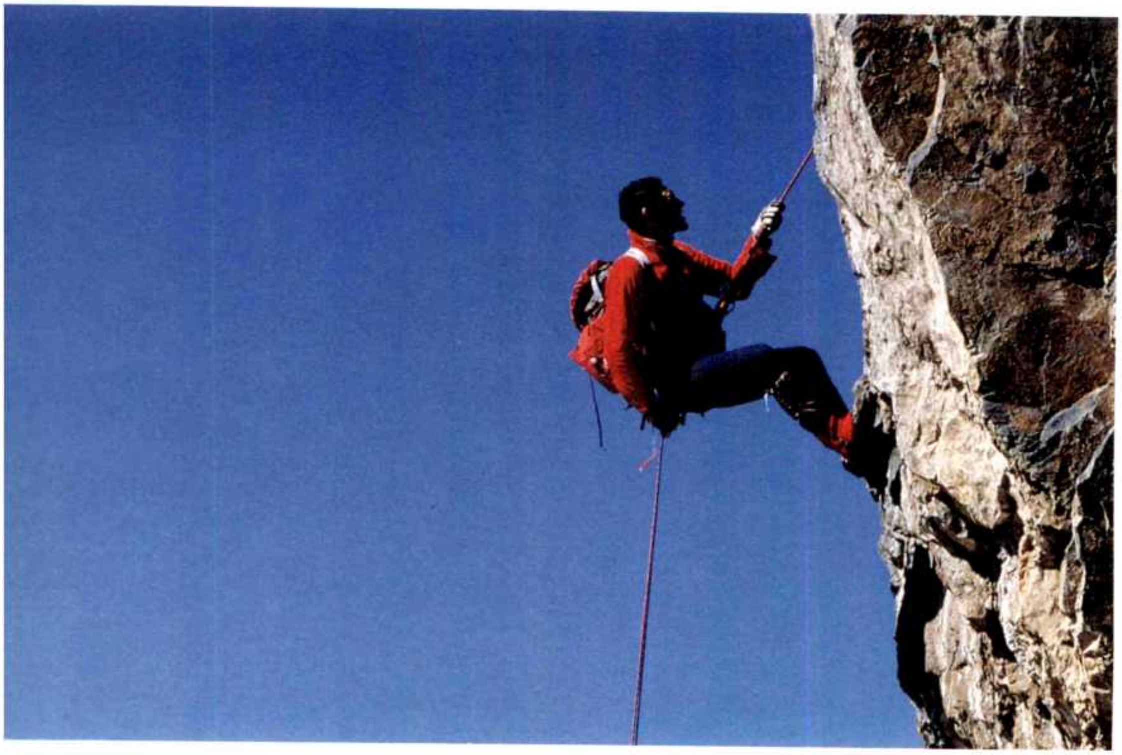

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 67, No. 3 SEPTEMBER 1991

EDITORIAL

PAIN AFTER SURGERY

It is well known that pain after surgery is not treated adequately in the majority of hospitals either in the United Kingdom or elsewhere in the world. Over the past few decades, many publications have attested to this fact; some articles have described the harrowing personal experiences of doctors who have undergone surgery [1, 2]; several editorials have been published in both specialized anaesthetic journals [3] and general medical journals [4, 5] lamenting this state of affairs, and attention has been drawn to inadequacy of pain relief after surgery by the majority of review articles on this subject [6, 7]. In the 1980s, surveys of patients' subjective well-being revealed an incidence of moderate or severe pain after surgery of 31–75% [8, 9]. What is so surprising is that this deplorable state of affairs has persisted and continues to persist in many hospitals, despite considerable advances in the pharmacology of analgesic drugs, and descriptions of new and improved methods of relieving pain.

Only in a few centres, populated by enthusiastic anaesthetists (and occasionally surgeons) has there been substantial improvement in the quality of postoperative pain relief in recent years. This trend has been most noticeable in the U.S.A., where acute pain teams have evolved at a remarkable rate since the first description of such a service was published in 1988 [10]. The reasons for this progress in North America, coupled with relative inactivity elsewhere, undoubtedly relate to the economics of health care delivery. In the United Kingdom and other countries which do not embrace a "fee for item of service" system, creation of an acute pain service has not commanded a high priority in relationship to other medical innovations and, consequently, progress has been hampered by inadequate funding of the resources required.

In this issue of the Journal, we report the first year's experience of an acute pain service which has been developed in a district general hospital in the U.K. [11]. Of particular interest is that the only major additional staffing requirement was the appointment of a nursing sister to spearhead development of the service. This is probably the minimal additional resource requirement in addition to equipment and increased input from the pharmacy, and reflects the particular workload, case mix, hospital layout and anaesthetic staffing of the unit described. It is certain that greater resources would be necessary in the absence of such a favourable conjunction of circumstances.

The general failure of the medical profession in the United Kingdom to achieve progress (despite good evidence that improvements in analgesia were attainable) stimulated the Royal College of Surgeons of England and the College of Anaesthetists to establish a working party to commission a report on pain after surgery. The Report was published in September 1990 and distributed to all Fellows of the Royal College of Surgeons of England and Fellows of the College of Anaesthetists in November 1990 [12]. The Report may be unfamiliar to other subscribers to this Journal and it may be valuable to summarize its contents.

The Working Party comprised representatives of the anaesthetic, nursing, surgical and pharmacy professions. The Report describes the extent of the problem of postoperative analgesia and reviews the well known reasons for failure of conventional parenteral administration of opioids to achieve satisfactory pain relief. It outlines all the methods which are available for treatment of acute pain and draws attention particularly to pain relief in children, noting that in children many of the traditional attitudes which exist towards pain in adults are exaggerated because of reluctance to prescribe adequate doses of opioids. The Report also draws attention to the role of an acute pain service, the problems of safety and monitoring, and the role of the high dependency unit.

The Report makes several important recommendations to improve education in analgesia, systematically record pain regularly after operation and establish acute pain teams in all major hospitals. It also makes important recommendations on the provision of staff, resources and facilities for the provision of adequate postoperative pain relief. It is composed in a style designed to be comprehensible to non-medically qualified administrators and other lay-persons. Although there may be very little new for the consultant anaesthetist within the United Kingdom, this Report nonetheless provides an extremely important and authoritative document which may be used by the profession to support a stated case of need for establishment of acute pain services and provision of other resources which are necessary.

We commend the Report of the Joint Colleges' Commission not only as a useful educational document for nursing, pharmacy, physiotherapy and other non-medical healthcare staff, but also to anaesthetists and surgeons for whom it should provide valuable ammunition in their fight for a share of resources. This Report should be useful, therefore, not only to anaesthetists within the United Kingdom, but also to those in other countries where resource allocation in health care delivery is similar to that in the U.K.

Graham Smith

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DOUBLE-BLIND COMPARISON OF THE MORPHINE SPARING EFFECT OF CONTINUOUS AND INTERMITTENT I.M. ADMINISTRATION OF KETOROLAC

J. W. BURNS, H. A. AITKEN, R. E. S. BULLINGHAM, C. S. McARDLE AND G. N. C. KENNY

SUMMARY

The morphine sparing effect of ketorolac 10 mg administered 4-hourly by intermittent i.m. injection was compared with a continuous i.m. infusion in a double-blind, placebo-controlled trial in patients undergoing upper abdominal surgery. During the 48-h postoperative period, each patient was provided with a patient-controlled analgesia (PCA) system which delivered bolus doses of morphine and administered the intermittent i.m. doses automatically via a computer controlled pump. In the first 24 h after surgery, there was a significant reduction in morphine demanded by both groups receiving ketorolac compared with placebo. Patients who received a continuous infusion of ketorolac after abdominal surgery required a median dose of morphine by PCA which was 49% less than controls. In the second 24 h and over the entire 48 h of the study, patients in the continuous group required significantly less morphine than those in the placebo group. The intermittent group used less than the placebo group, but this was not significant.

KEY WORDS

Analgesia: postoperative, PCAS. Analgesics: ketorolac, morphine.

Patient controlled analgesia (PCA) provides better postoperative analgesia, as each patient determines the appropriate dose of analgesic necessary to produce acceptable pain relief [1]. If the patient is provided with morphine on demand from a PCA system, the analgesic efficacy of supplementary non-opioid analgesics and of techniques such as suggestion during anaesthesia may be determined objectively by measuring the reduction in morphine requirements compared with patients receiving placebo [2–4].

Ketorolac is a new non-opioid analgesic which has been shown in some studies to have analgesic activity which was not significantly different from that of morphine and pethidine [5, 6]. It has been used successfully in the treatment of postoperative orthopaedic pain [7, 8], and other types of acute pain. A previous placebo controlled study [9] using PCA has confirmed the analgesic potency of ketorolac following upper abdominal surgery. The present study was designed to compare the efficacy of intermittent with continuous administration of ketorolac during the first 48 h after upper abdominal surgery.

PATIENTS AND METHODS

We studied patients aged 18–75 yr, weighing 40–95 kg, undergoing elective upper abdominal surgery. Patients with respiratory insufficiency, hepatic or renal impairment, or those known to abuse alcohol or drugs were excluded. The study was approved by the hospital Ethics Committee and conducted under a clinical trials exemption certificate. All patients were visited before surgery, the nature of the study explained, and written informed consent obtained.

All patients were premedicated with temazepam 20–40 mg orally; anaesthesia was induced with

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TABLE I. *Administration of drugs. All patients received a continuous i.m. infusion together with computer controlled i.m. injections every 4 h in the sequence shown*

Patient group	Intermittent injection	Continuous infusion
Continuous	Placebo	Ketorolac
Intermittent	Ketorolac	Placebo
Placebo	Placebo	Placebo

thiopentone 3–6 mg kg^{-1} and maintained with nitrous oxide and enflurane in oxygen, with supplements of alfentanil as required.

At the end of surgery, patients were allocated randomly to receive one of three regimens (table I): a continuous i.m. infusion of ketorolac with intermittent injections of placebo (continuous group), intermittent i.m. injections of ketorolac with continuous infusion of placebo (intermittent group) or continuous and intermittent administration of placebo (placebo group). The continuous infusion was delivered by a Graseby Dynamics battery-powered syringe driver and the intermittent bolus doses by a computer controlled Braun Perfusor Secura syringe driver. Both were administered i.m. via a non-return valve into the deltoid through a 22-gauge Teflon cannula inserted in one site. Medications were identical in appearance and thus the study was conducted double-blind.

Continuous ketorolac group

Patients received a continuous i.m. infusion of ketorolac at a loading dose of 12.5 mg h^{-1} for 30 min and at 2.5 mg h^{-1} for the remainder of the study. The initial faster rate was designed to achieve a steady state concentration more rapidly. In addition, they received also intermittent i.m. injections of saline every 4 h under automatic computer control.

Intermittent ketorolac group

Patients received computer controlled intermittent i.m. injections of ketorolac 10 mg 4-hourly, together with a continuous i.m. infusion of saline administered as for the continuous group.

Placebo group

The placebo group received intermittent injections and continuous infusions of saline.

Immediately after the end of surgery, all three groups of patients were connected to the i.m. ketorolac delivery systems and to a PCA apparatus from which they were able to obtain i.v. bolus doses of morphine. The PCA system consisted of a standard Apple IIe microcomputer which was linked to an Imed 929 computer controlled infusion pump [10]. Data were stored automatically on magnetic disc for analysis later. This PCA system permitted the patient to signal to the machine when analgesia was required, by pressing a hand-held button twice within 1 s. A bolus dose of morphine 0.02 mg kg^{-1} was delivered i.v. by the Imed pump with a "lock-out" time of 2 min. The Apple IIe computer also controlled a Braun Perfusor Secura syringe pump. This injected automatically every 4 h the intermittent i.m. dose of either ketorolac or saline.

Pain was measured using 100-mm visual analogue scores at 2–6 h after the start of the study (day 0), and on the morning and afternoon of postoperative day 1 and day 2.

Patient data were analysed using Student's *t* test or chi-square test as appropriate. Morphine consumption and visual analogue pain scores were analysed using repeated measures analysis of variance.

RESULTS

Sixty-seven patients entered the study; 63 completed 24 h of the study satisfactorily and 61 completed the entire study. The magnetic disc used to store data from one patient in the continuous group was damaged and the data lost. Two patients were withdrawn from the continuous and one from the intermittent group during the first 24 h of the study because of machine failure. One patient was withdrawn from the intermittent group on request at 36 h and one from the continuous group at 34 h because the i.v. cannula was removed inadvertently. All patients who were withdrawn from the study received

TABLE II. *Patient data (mean (range or* SD*)).* $^{*}P < 0.05$

	Continuous	Intermittent	Placebo
Sex (M/F)	9/10	10/13	10/11
Age (yr)	47.2*	48.6*	56.1
	(27–71)	(23–68)	(42–68)
Weight (kg)	63.5	62.7	68.3
	(9.6)	(12.1)	(12.0)
Surgical procedure			
Cholecystectomy	11	13	12
Gastric surgery	6	5	4
Miscellaneous	2	5	5

TABLE III. *Consumption of morphine (median and range).* ** $P < 0.01$; *** $P < 0.001$ *compared with placebo*

	Morphine consumption (mg)		
	Continuous group	Intermittent group	Placebo group
First 24 h	48 (25–137)*** ($n = 19$)	74 (22–130)** ($n = 23$)	95 (22–198) ($n = 21$)
Second 24 h	26 (1–74)*** ($n = 18$)	32 (2–102) ($n = 22$)	44 (2–113) ($n = 21$)
Total over 48 h	80 (31–211)*** ($n = 18$)	111 (31–221) ($n = 22$)	139 (43–258) ($n = 21$)

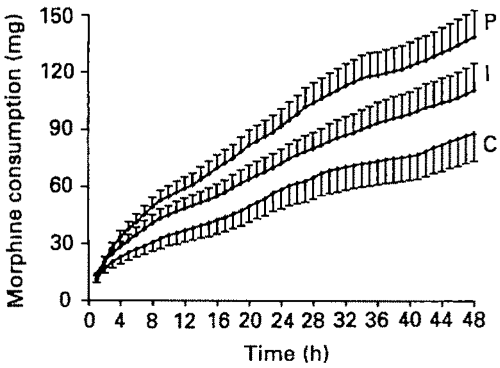

FIG. 1. Cumulative morphine consumption of patients receiving placebo (P), intermittent (I) or continuous (C) ketorolac for 48 h after upper abdominal surgery (mean, SEM).

TABLE IV. *Visual analogue pain scores (median and range) (no significant differences between groups)*

	Pain score (mm)		
	Continuous group	Intermittent group	Placebo group
2–6 h	39.5 (3–88)	31.0 (5–83)	48.5 (7–82)
09:00 day 1	24.0 (6–98)	16.5 (1–99)	32.0 (4–93)
Afternoon day 1	26.5 (0–79)	21.0 (2–61)	24.0 (5–82)
09:00 day 2	13.0 (0–40)	12.5 (0–61)	25.0 (1–68)
Afternoon day 2	14.0 (0–36)	18.0 (0–54)	23.0 (0–67)

TABLE V. *Distribution of the most frequent side effects*

	Continuous group	Intermittent group	Placebo group
Nausea/vomiting	3	5	4
Urinary retention	3	1	2
Injection site pain	2	3	0

intermittent i.m. morphine administered as required. There were no withdrawals from the study because of adverse events. Patients who received ketorolac were significantly younger than those who received placebo ($P < 0.05$), but there were no differences in sex or weight between the groups (table II).

The morphine requirements of patients in the continuous ($P < 0.001$) and intermittent ($P < 0.01$) groups were significantly less during the first 24 h after operation compared with the placebo group (table III, fig. 1). The continuous group used significantly less morphine during the second 24 h and also during the entire 48-h study period compared with placebo ($P < 0.001$). While the intermittent group required less morphine than the placebo group during the second 24-h period and over the total 48 h of the study, this difference was not significant.

Median visual analogue pain scores of patients who received ketorolac were less than those receiving placebo (ns) (table IV).

The most common side effects were nausea or vomiting and urinary retention (table V), but there were no differences between the groups. Five of the 46 patients who received ketorolac complained of pain at the injection site, but this was mild in nature and no patient requested to be withdrawn because of this discomfort.

DISCUSSION

Ketorolac does not alter the ventilatory response to increasing concentrations of inspired carbon dioxide [11]. The results of a study of patients undergoing minor surgical procedures demonstrated lack of cardiorespiratory effects after administration of ketorolac 30 mg, but the expected depression of respiration occurred after a bolus dose of alfentanil 0.5 mg [12]. Ketorolac may, therefore, provide useful analgesia, either alone or as a supplement to an opioid, with minimal depressant effects.

The younger mean age of patients who received ketorolac in the present study would be expected to increase their morphine demands [1], but both ketorolac groups required less morphine compared with the placebo group. However, in the first 24 h the morphine sparing effect was greater for those patients given the continuous infusion. During the second 24 h of the study, patients in the intermittent group required less morphine compared with the placebo group, but this difference was not significant. Patients who received the same rate of dosing of ketorolac, but administered by a continuous infusion instead of intermittent doses, did show a significant morphine sparing effect during the second 24-h period compared with placebo. Over the entire 48-h duration of the study, the intermittent group used less morphine than the placebo group (ns). However, there was a significant reduction in morphine requirements in the group which received a continuous infusion of ketorolac.

The improvement in morphine sparing effect with the continuous mode of infusion occurred possibly because, during the periods of low plasma concentrations inherent in an intermittent dosing regimen, there was a decrease in analgesic efficacy for which extra morphine was required in compensation. The use of a larger intermittent dose or more frequent administrations may have resulted in improved efficacy. However, more frequent i.m. injections would not be favoured by the patient or the nursing staff, and the use of larger doses would cause greater peak concentrations of the drug, which may increase the incidence of any adverse effects such as gastric irritation. Therefore, a method of providing continuous delivery of the drug would seem to be useful in this situation.

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DISPOSITION OF MEPIVACAINE AND BUPIVACAINE ENANTIOMERS IN SHEEP†

L. E. MATHER

SUMMARY

Mepivacaine and bupivacaine are used clinically as racemic mixtures of enantiomers. In these studies the enantiomers of each agent were administered separately to sheep by i.v. bolus injection on separate occasions. Enantioselective disposition was deemed if the R:S ratio of the relevant pharmacokinetic parameter differed significantly from unity. Both enantiomers of both agents were cleared principally by the liver; urinary excretion of unmetabolized agents accounted for < 2% of the doses. For R(−)- and S(+)-mepivacaine, respective mean (SEM) values of parameters were: total body clearance 1.20 (0.29) litre min^{-1} and 0.97 (0.20) litre min^{-1} (ns); total volume of distribution 144 (39) litre and 80 (21) litre ($P < 0.05$); slow half-life 120 (40) min and 84 (22) min (ns); mean hepatic extraction ratio 0.50 (0.14) and 0.52 (0.09) (ns); mean hepatic clearance 0.75 (0.23) litre min^{-1} and 0.75 (0.18) litre min^{-1} (ns). For R(+)- and S(−)-bupivacaine, respective values were: total body clearance 0.77 (0.33) litre min^{-1} and 0.53 (0.26) litre min^{-1} ($P < 0.05$); total volume of distribution 40 (10) litre and 43 (10) litre (ns); slow half-life 57 (10) min and 104 (21) min ($P < 0.05$); mean hepatic extraction ratio 0.46 (0.15) and 0.29 (0.13) ($P < 0.05$); mean hepatic clearance 0.85 (0.31) litre min^{-1} and 0.54 (0.26) litre min^{-1} ($P < 0.05$). Thus there was enantioselective distribution of mepivacaine and enantioselective clearance of bupivacaine, but the magnitude of the effect was relatively small.

KEY WORDS

Anaesthetics, local: mepivacaine, bupivacaine. Biotransformation stereoisomers Pharmacokinetics: extraction ratio.

Many drugs contain one or more chiral centres and exist as racemates (i.e. as equal amounts of optically active stereoisomeric forms or enantiomers). Clinical anaesthesia may involve the use of several such drugs, for example halothane, thiopentone, methadone. If the pharmacokinetics of the enantiomers differ (as is often the case), the time course of measured blood drug concentrations after administration of a racemate consists of a time-dependent mixture of enantiomers [1] but, because most drug assays are not enantioselective, this may not be apparent. The clinical implication of this depends probably on the relative intrinsic pharmacodynamic properties of the enantiomers [2, 3]. Whereas one enantiomer (the eutomer) may be the principal agonist, the other (the distomer) may range from being practically equivalent in potency to the eutomer, to being antagonistic. The situation is more complicated when the metabolic pathways and the activities of the metabolites are considered also [1].

The homologous aminoacylaniline local anaesthetic agents mepivacaine and bupivacaine are used as racemates [4–7]. In most older literature, the enantiomers of these agents are described by the L- and D-nomenclature (as determined by their stereochemical configuration relative to glyceraldehyde) and designated with the sign of their rotation of plane polarized light. Thus R(−)-, S(+)- and RS(racemic)-mepivacaine are also referred to, respectively, as D(−), L(+) and DL(±)-mepivacaine and R(+)-, S(−)- and RS-

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† This paper is dedicated to the memory of friend and colleague Dr Peter J. Meffin (1943–1987), who made major contributions to our knowledge of the disposition of mepivacaine and of other enantiomeric drugs before his untimely death.

bupivacaine have been referred to, respectively, as D(+)-, L(−)- and DL(±)-bupivacaine. Lignocaine does not contain a chiral centre, whereas prilocaine [8] and etidocaine [9] both contain chiral centres and are used as racemates. Ropivacaine contains a chiral centre, but is made and used as the single enantiomer S-(−)-1-propyl-2′, 6′pipecoloxylidide hydrochloride monohydrate [10].

Some local anaesthetic agents demonstrate enantioselective differences of effect in nerve blocking bioassays *in vivo*. For example, the duration of infiltration anaesthesia was found to be longer from the S-enantiomers of both mepivacaine and bupivacaine than from the RS- and R-enantiomers [6]. Because enantiomeric differences are not usually seen in nerve blocking bioassays *in vitro*, those observed *in vivo* have been rationalized as differences in rates of systemic uptake from the sites of drug deposition [6, 8]. Similarly, enantioselective differences in toxicity of these agents [6] have been rationalized in terms of differences in vascular effects and in systemic and regional pharmacokinetics of agents [6, 11–14].

As part of a continuing investigation into the systemic and regional pharmacokinetics of local anaesthetic agents in sheep [15,16], the present studies were performed to provide information about the disposition of the enantiomers of mepivacaine and bupivacaine when administered separately. A companion paper [17] reports the disposition of the enantiomers of bupivacaine when administered simultaneously as the clinically used racemate.

MATERIALS AND METHODS

Study design

Twenty-four studies were performed in seven sheep which had been prepared previously with appropriate catheters to determine the systemic and regional drug disposition. The studies were approved by the local institutional Ethics Committee. The preparation, its physiological profile and analogous previous applications have been reported in detail [14–18]; only those aspects relevant to this study are described here.

Merino ewes aged 1–2 yr and of mean weight 43 (SEM 2) kg were prepared for study by the insertion, under general anaesthesia, of polyethylene catheters with the tips in the right atrium for the administration of drugs, indicator substances and i.v. crystalloid and at the aortic arch and in a right hepatic vein for sampling of blood. At least 1 week elapsed between catheter insertion and study. As described previously, right atrial infusions of sodium bromsulphthalein (BSP) were made to measure hepatic blood flow using the Fick technique. In three animals treated with each agent, cardiac output was measured also by thermodilution at the times of taking blood samples, for 120 min after administration of drug.

Bolus doses of the individual enantiomers of mepivacaine and of bupivacaine (as hydrochloride salts) were administered via the right atrial catheter on separate occasions. In the absence of information demonstrating a relationship between total body weight and pharmacokinetic variables, doses of the enantiomers (approximately 40 mg, known accurately) were chosen to maximize the usefulness of the very small quantities of the agents that were available, whilst still providing readily measurable blood concentrations of drugs. In one study, residual 14-mg doses of the bupivacaine enantiomers were used in one sheep.

Drug analysis

Blood (1.0 ml) was sampled from each of the catheters immediately before injection (blank) and, if possible, at 1, 3, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 120, 150, 180 and 240 min (exact times known) after injection. In some studies, urine was collected for 48 h after injection. Because the enantiomers were administered independently, it was possible to perform non-enantioselective blood and urine assays for the concentrations of local anaesthetic agents after solvent extraction by gas–liquid chromatography with nitrogen selective detection [15].

A newly developed high pressure liquid chromatographic column, capable of performing chiral separations [19] of these agents, was used to assay both the enantiomeric purity of the agents as administered and the blood concentrations of each agent in one animal, to examine the possibility of enantiomeric inversion *in vivo*. Assay of the agents was made by direct application of the drug solution for injection onto the column; assay of blood drug concentrations was made after solvent extraction using the method devised for procainamide [20]. In both cases the column stationary phase consisted of α_1-acid glycoprotein (Chirasil AGP; ChromaTech, Sweden); the mobile phase consisted of disodium monohydrogen phosphate

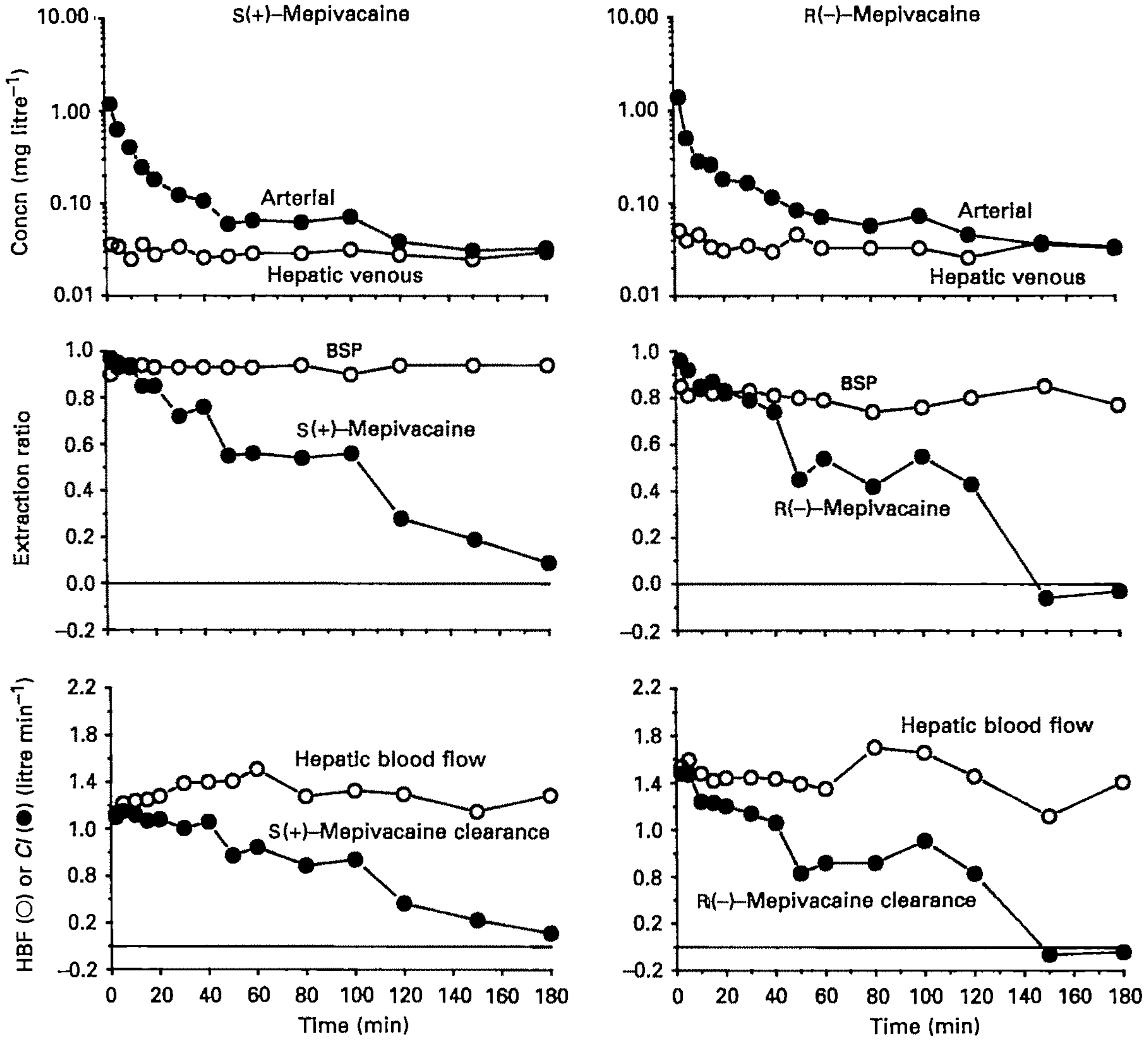

FIG. 1. Left panels: S(+)-Mepivacaine; right panels: R(–)-mepivacaine: both after right atrial injection in the same sheep. Top: Regional blood concentrations. Middle: Hepatic extraction ratios of mepivacaine and BSP. Bottom: Hepatic blood flow (HBF) and hepatic clearance (*Cl*) of mepivacaine.

0.01 mol litre^{-1}: 2-propanol (94:6) containing sodium chloride 0.05 mol litre^{-1} and N,N-dimethyl octylamine 200 mg litre^{-1} at pH 7.0, at a flow rate of 0.7 ml min^{-1}, with detection at 214 nm. Internal standards were chosen as the corresponding enantiomer of the alternative drug. Under the conditions of the assay, the retention times of R(–)- and S(+)-mepivacaine were, respectively, 5.9 and 7.0 min; those of R(+)- and S(+)-bupivacaine were, respectively, 12.7 and 15.6 min. This method has now superseded that reported in our companion paper [17]. Although the assay statistics (CV ≈ 5 %) are similar, more than 1000 samples have been analysed satisfactorily with good peak symmetry with this column.

Pharmacokinetic analysis

The arterial blood enantiomer concentration–time data were fitted with bi-exponential decay curves using the extended least squares non-linear regression program MKMODEL Version 3.34 on a personal computer. From these, the systemic disposition parameters, mean total body clearance (*Cl*), initial dilution volume (*V*), the volume of distribution at steady state equilibrium (V^{ss}) and

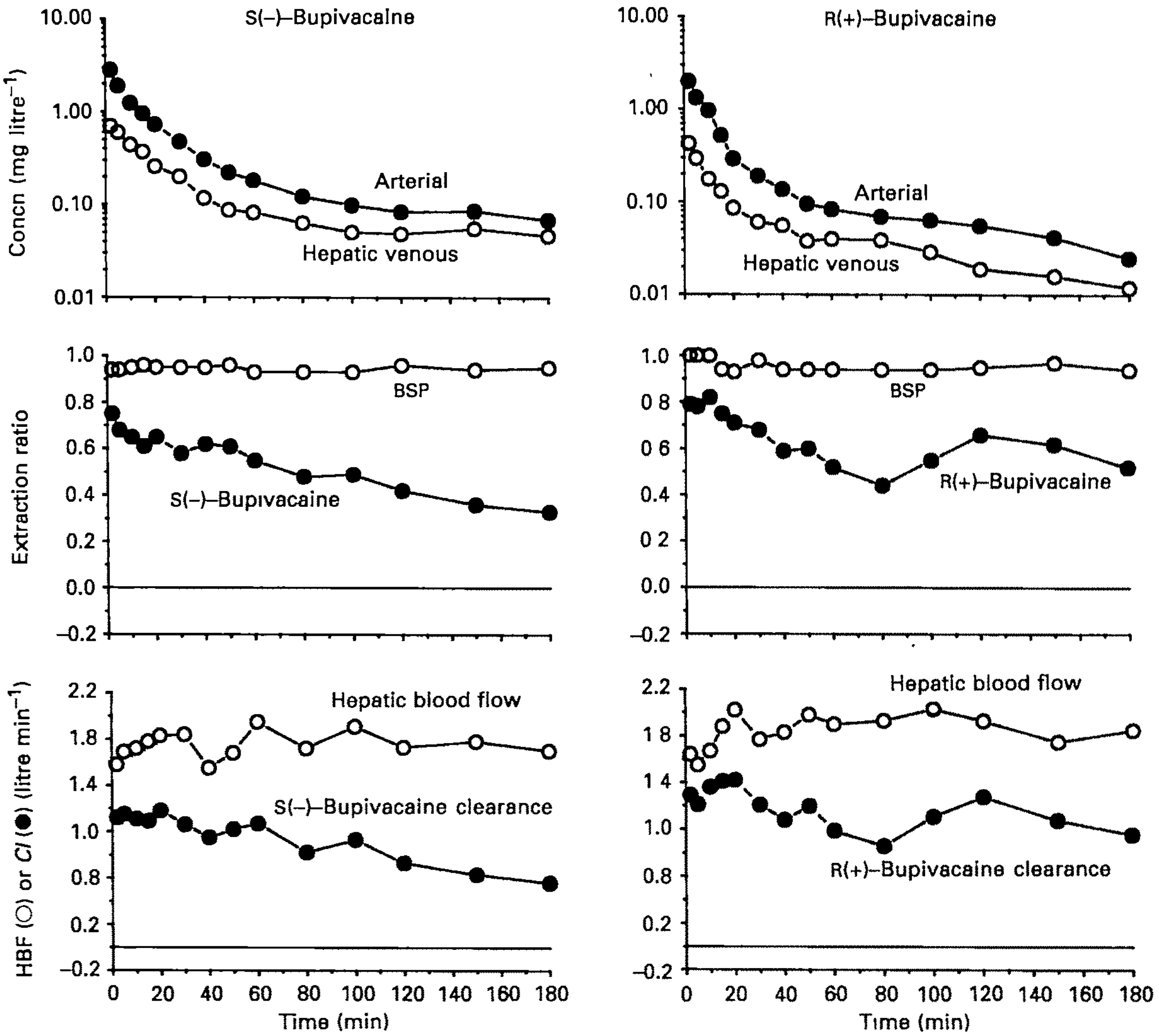

FIG. 2. Left panels: s(−)-Bupivacaine; right panels: r(+)-bupivacaine; both after right atrial injection in the same sheep. Top: Regional blood concentrations. Middle: Hepatic extraction ratios of bupivacaine and BSP. Bottom: Hepatic blood flow (HBF) and hepatic clearance (*Cl*) of bupivacaine.

fast and slow half-lives (respectively, $T_{\frac{1}{2}}^{f}$ and $T_{\frac{1}{2}}^{s}$) were obtained by routine non-compartmental methods [21]. The time-averaged hepatic extraction ratios of the drugs were obtained from the arterial and hepatic venous areas under the drug concentration–time curves extrapolated to infinity (AUC) as described previously [20]. Time-averaged hepatic drug clearances (Cl_{H}) were obtained from the products of the time-averaged blood flows (HBF) and the extraction ratios (ER_{H}). The binding of the drugs was determined in drug-free plasma pooled from three sheep. The equilibrium dialysis method of La Rosa, Mather and Morgan [22] was used with initial drug concentrations of 0.5, 2 and 10 mg litre^{-1} in pH 7.4 phosphate buffer at 37 °C.

The total volume of distribution of unbound drug (Vu^{ss}) was calculated from the ratio of the average V^{ss} to the average unbound drug fraction in plasma. Similarly, the mean total body clearance of unbound drug (*Clu*) was calculated from the ratio of the average mean total body clearance to the average unbound drug fraction in plasma. These were used to determine the influence of drug binding on drug distribution and elimination, respectively.

TABLE I. *Disposition of mepivacaine enantiomers in the sheep. Mean* (SEM) *of six cross-over studies except*: †n = 5; ‡n = 3. **Significant enantiomeric bias* R:S ≠ 1 (P < 0.05)

	R(−)	S(+)	R:S Ratio
Mean total body clearance (litre min^{-1})	1.20 (0.29)	0.97 (0.20)	1.31 (0.32)
Initial dilution volume (litre)	12 (5)	15 (3)	1.22 (0.31)
Total volume of distribution (litre)	144 (39)	80 (21)	1.99 (0.51)
Fast half-life (min)	4 (1)	5 (2)	1.33 (0.38)
Slow half-life (min)	120 (40)	84 (22)	1.66 (0.48)*
Mean hepatic extraction ratio†	0.50 (0.14)	0.52 (0.09)	1.15 (0.43)*
Mean hepatic clearance (litre min^{-1})†	0.75 (0.23)	0.75 (0.18)	1.19 (0.46)
Urinary excretion in 24 h (% dose)‡	1.1 (0.4)	2.1 (0.4)	0.6 (0.2)
Mean renal clearance (ml min^{-1})‡	3 (1)	8 (6)	0.5 (0.4)
Mean total body clearance of unbound drug (litre min^{-1})	≈ 3.9	≈ 3.8	≈ 1.0
Mean total volume of distribution unbound drug (litre)	≈ 450	≈ 320	≈ 1.4

TABLE II. *Disposition of bupivacaine enantiomers in the sheep. Mean* (SEM) *of six cross-over studies except*: †n = 5; ‡n = 3. **Significant enantiomeric bias* R:S ≠ 1 (P < 0.05)

	R(+)	S(−)	R:S Ratio
Mean total body clearance (litre min^{-1})	0.77 (0.33)	0.53 (0.26)	1.65 (0.14)*
Initial dilution volume (litre)	20 (5)	15 (3)	1.33 (0.20)
Total volume of distribution (litre)	40 (10)	43 (10)	0.93 (0.08)
Fast half-life (min)	6 (1)	6 (1)	1.46 (0.54)
Slow half-life (min)	57 (10)	104 (21)	0.56 (0.30)*
Mean hepatic extraction ratio†	0.46 (0.15)	0.29 (0.13)	2.16 (0.45)*
Mean hepatic clearance (litre min^{-1})†	0.85 (0.31)	0.54 (0.26)	2.15 (0.29)*
Urinary excretion in 24 h (% dose)‡	0.10 (0.06)	0.13 (0.09)	1.0 (1.4)
Mean total body clearance of unbound drug (litre min^{-1})	≈ 3.9	≈ 2.7	≈ 1.4
Mean total volume of distribution unbound drug (litre)	≈ 202	≈ 213	≈ 1.0

Statistical analysis

The R:S ratios of the respective pharmacokinetic parameters were transformed logarithmically to produce a normal distribution. Enantiomeric differences were determined by one-sample *t* testing of the logarithmically transformed values against a value of 0. Comparisons between unbound fractions of the enantiomers in plasma were performed using Student's *t* test for paired data. Two-tailed probabilities of $P < 0.05$ were considered significant.

RESULTS

When assayed enantioselectively, the drug solutions, as administered, contained no detectable contamination by the other enantiomer. Similarly, by assay for blood concentration of drug, there was no evidence of inversion of the enantiomers *in vivo*.

Data sets from one animal having a complete cross-over of the enantiomers of mepivacaine and bupivacaine are shown in figures 1 and 2. After each dose, the arterial blood drug concentration–time data displayed biphasic curves when plotted on log-linear co-ordinates and were fitted appropriately with bi-exponential decay equations.

Enantioselectivity of mepivacaine disposition

From the data presented in table I, it may be seen that there were no systematic enantiomeric biases in Cl, V, $T_{\frac{1}{2}}^{1}$ or $T_{\frac{1}{2}}^{z}$; however V^{ss} of R(−)-mepivacaine exceeded that of S(+)-mepivacaine ($P < 0.05$). Although measured in only three animals, small fractions of the doses of both enantiomers were excreted unchanged into urine, where renal clearance of R(−)-mepivacaine was approximately twice that of S(+)-mepivacaine.

TABLE III. *Mean cardiac output* (SEM) *during the first 15 min and the subsequent 105 min after i.v. injection of 40 mg of each of the enantiomers of mepivacaine and bupivacaine in each of three sheep on separate occasions*

Enantiomer	Sheep No.	Cardiac output (litre min^{-1}) 0–15 min	15–120 min
R(−)-Mepivacaine	1	5.9 (0.5)	5.9 (0.2)
	2	5.4 (0.3)	5.1 (0.1)
	3	4.9 (0.2)	4.7 (0.1)
S(+)-Mepivacaine	1	5.4 (0.1)	5.6 (0.2)
	2	5.6 (0.1)	5.1 (0.1)
	3	4.7 (0.2)	5.3 (0.2)
R(+)-Bupivacaine	2	6.6 (0.4)	5.6 (0.2)
	3	3.6 (0.1)	3.6 (0.1)
	4	7.6 (0.2)	7.3 (0.1)
S(−)-Bupivacaine	2	5.4 (0.1)	5.2 (0.2)
	3	3.7 (0.1)	4.1 (0.1)
	4	6.4 (0.3)	6.8 (0.1)

TABLE IV. *Binding of the enantiomers of mepivacaine and bupivacaine in pooled sheep plasma. Mean* (SD) *values of three replicate determinations. Differences between enantiomers:* **$P < 0.01$; ***$P < 0.001$

Initial buffer concn (mg litre^{-1})	Enantiomer bound (%) Mepivacaine S(+)-	R(−)-	Bupivacaine S(+)-	R(+)-
0.5	77 (2)**	68 (1)**	81 (3)	80 (2)
2.0	74 (1)***	68 (0)***	84 (3)	79 (3)
10	55 (3)	55 (1)	65 (3)	67 (1)

There was no clear evidence for enantioselectivity in ER_H or Cl_H. Of interest was an apparent time-dependence of ER_H (fig. 1) which, almost invariably, decreased over the study period from a value near unity to near zero, in the presence of an essentially constant HBF and a constant ER_H of BSP.

Enantioselectivity of bupivacaine disposition

The *Cl* of R(+)-bupivacaine was greater than that of S(−)-bupivacaine ($P < 0.05$) (table II). As there was no enantiomeric bias in V^{ss}, $T_{\frac{1}{2}}^{z}$ of S(−)-bupivacaine was longer than that of R(+)-bupivacaine ($P < 0.05$) (table II). Both ER_H and Cl_H of R(+)-bupivacaine were greater than the corresponding values for S(−)-bupivacaine. Although there was evidence of a time-dependent decrease in ER_H (fig. 2), it was not as extensive as with mepivacaine (fig. 1). Only negligible quantities of each enantiomer were excreted unchanged into urine and there were no enantioselective trends in renal clearance.

Enantioselectivity of toxic effects of bupivacaine

There was a clear difference in the CNS toxicity of the enantiomers of bupivacaine. In every case, administration of the 40-mg (nominal) dose of R(+)-bupivacaine was attended by convulsions, starting at 15–45 s and lasting for 1.5–3 min after injection. Convulsions did not occur with similar doses of S(−)-bupivacaine when administered to the same animals. In the animals in which cardiac output was measured, the mean cardiac output did not differ systematically between the "convulsive period" and the ensuing 105 min (table III).

Enantioselectivity and relevance of drug plasma binding

The plasma binding of mepivacaine was less than that of bupivacaine at all three drug concentrations studied (table IV). While there was no evidence of enantioselectivity of bupivacaine binding, there was greater binding of S(+)- than of R(−)-mepivacaine at the initial concentrations of 0.5 mg litre^{-1} ($P < 0.01$) and 2.0 mg litre^{-1} ($P < 0.001$).

Based upon the average mean values of V^{ss} derived from table I (S(+)- and R(−)-mepivacaine = 80 and 144 litre, respectively; S(−)- and R(+)-bupivacaine = 43 and 40 litre, respectively) and the average unbound drug fractions in plasma, derived from table IV (S(+)- and R(−)-mepivacaine = 0.25 and 0.32, respectively; S(−)- and R(+)-bupivacaine both = 0.20), the average values of Vu^{ss} of S(+)- and R(−)-mepivacaine were 320 and 450 litre, respectively, suggesting enantioselective bias; those of S(−)- and R(+)-bupivacaine were 213 and 202 litre, respectively. Similarly, based upon the average mean values of *Cl* derived from table I (S(+)- and R(−)-mepivacaine = 0.97 and 1.20 litre min^{-1}, respectively; S(−)- and R(+)-bupivacaine = 0.54 and 0.78 litre min^{-1}, respectively) and the average unbound drug fractions in plasma derived from table IV, the average values of *Clu* of S(+)- and R(−)-mepivacaine were 3.9 and 3.8 litre min^{-1}, respectively; those for S(−)- and R(+)-bupivacaine were 2.7 and 3.9 litre min^{-1}, respectively, suggesting enantioselective bias.

DISCUSSION

Although there have been many studies of the pharmacokinetics of mepivacaine and bupivacaine, there has been little recognition of the fact that racemic agents were being administered and treated as being single entities. In fairness, the principal reason for this has been the lack, until now, of suitable methods for enantioselective analysis of these agents. In a particularly cogent review [1], it was pointed out that ignorance of pharmacokinetic enantioselectivity may lead to misinterpretation of data, especially when blood drug concentration–pharmacological response data and comparisons of species or patients are involved. For example, a blood concentration of a drug associated with toxicity in one subject might not be so in another subject if the enantiomeric composition differed.

This study was intended to provide comparative data on the total body and regional pharmacokinetics of the enantiomers of mepivacaine and bupivacaine when administered independently. Because of the possibility of interactions between enantiomers, further studies to determine the pharmacokinetics of the enantiomers when the clinically-used bupivacaine racemate was administered were carried out and are reported separately [17].

Some indications of enantioselectivity were found, but the magnitude of the effects was small. First, the estimates of V^{ss} and Vu^{ss} of R(−)-mepivacaine were both greater than those of S(+)-mepivacaine. This is consistent with a greater tissue affinity of R(−)-mepivacaine. However, there were no enantiomeric differences in *Cl* or Cl_H (table I). Second, the estimates of both *Cl* and *Clu* of R(+)-bupivacaine were greater than those of S(−)-bupivacaine (table II). This was consistent with a greater ER_H and Cl_H, presumably because of a more favourable metabolic enzyme–substrate relationship of the R(+)-enantiomer. In contrast, there were no enantioselective differences in bupivacaine distribution, or in plasma binding. In the bupivacaine studies, the mean time-averaged Cl_H was similar to the mean *Cl*, but in the mepivacaine studies it was somewhat less.

The apparent time-dependence of ER_H is intriguing. A distribution-based time-dependent extraction ratio would be expected as blood–tissue equilibration is satisfied but, with a putative time constant of about 1 min for a high perfusion organ such as the liver, this should be satisfied within about 10 min, thereafter resulting in an essentially constant extraction ratio. A similar time-dependence of ER_H has been reported for lignocaine in rat liver *in vitro*, where it has been attributed to metabolic inhibition because of local accumulation of a metabolite [23]. These agents undergo complex metabolism [24–26]. Because the clearance decreases with time (i.e. with decreasing drug concentration) this mechanism also is possible in the present instance, although there was no evidence of time-dependent Cl_H during infusion of the racemate [17].

At the doses of mepivacaine used, the enantiomers did not cause overt pharmacological effects, although differences in toxicity between enantiomers have been found in laboratory rodents with greater doses [6]. The finding of greater convulsant activity of R(+)-bupivacaine confirms observations made in rabbits in which the mean convulsive dose of R(+)-bupivacaine was approximately 50% that of S(−)-bupivacaine [6]. The induction of convulsions has been reported to cause a smaller *Cl* of racemic mepivacaine and, possibly, of bupivacaine [27], although the interpretation of these findings has not been attempted in terms of enantioselectivity. That the induction of convulsions alone was not responsible for the enantioselective differences in bupivacaine clearance cannot be dismissed but, from similar enantioselective differences found in *Cl* in the study with the 14-mg doses of bupivacaine in which there was no convulsive response, and from the companion study involving infusion of the racemate [17], it seems unlikely to be the main reason. Although cardiac output increases markedly with supraconvulsive doses [28], it is clear from table III and figure 2 that, in this study, convulsions were not attended by a concomitant significant increase in cardiac output and in hepatic blood flow with a corresponding increase in drug clearance. No data could be found concerning the relative cardiotoxic effects of the enantiomers.

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CARDIOVASCULAR EFFECTS AND REGIONAL CLEARANCES OF I.V. BUPIVACAINE IN SHEEP: ENANTIOMERIC ANALYSIS

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SUMMARY

All currently available aminoacylaniline local anaesthetics, except lignocaine, contain a chiral centre but are used as racemates, a fact usually ignored in pharmacokinetic studies. This study reports the cardiovascular effects, and the regional and total body clearances of the enantiomers of bupivacaine determined at two steady state periods (3–4 h and 23–24 h) during continuous i.v. infusion to subtoxic concentrations in conscious sheep. Racemic (RS)-bupivacaine hydrochloride 1 mg min^{-1}, was infused in five sheep that had been prepared at least 1 week previously with appropriate intravascular cannulae. The infusion of RS-bupivacaine produced constant arterial R(+)- and S(−)-bupivacaine concentrations of 0.20–0.68 mg litre^{-1} and 0.22–0.94 mg litre^{-1}, respectively. This caused no appreciable cardiovascular effects. The hepatic clearance of R(+)- was greater than that of S(−)-bupivacaine ($P < 0.05$) with mean (SD) clearance at the two respective time periods being 1.37 (0.78) and 1.47 (0.57) litre min^{-1} and 1.01 (0.72) and 1.29 (0.47) litre min^{-1}. There was no significant clearance of either enantiomer by the lungs, brain, heart, gut, kidneys or hindquarters. It was concluded that, although the clearances of the enantiomers differed, the total body clearance of both enantiomers was accounted for by hepatic clearance exclusively. There was no evidence of time dependent kinetics.

KEY WORDS

Anaesthetics local: bupivacaine, stereoisomers. Blood flow: regional. Pharmacokinetics: bupivacaine, extraction ratio, regional clearance.

An accompanying report from our laboratory [1] has re-emphasized that the aminoacylaniline local anaesthetic agents mepivacaine, prilocaine, bupivacaine and etidocaine contain a chiral centre and thus can exist as a pair of stereoisomers or enantiomers, designated R- and S- configurations according to the Sequence Rule of Cahn, Ingold and Prelog [2]. Nevertheless, these agents are prepared and used clinically as the racemate despite the fact that, in most instances, differences exist in the pharmacodynamics and pharmacokinetics of such enantiomers. For example, although the enantiomers of bupivacaine are equipotent in producing neural block *in vitro*, R(+)-bupivacaine is more toxic than S(−)-bupivacaine after s.c. or i.v. administration [3]. However, S(−)-bupivacaine produces a longer duration of anaesthesia [3]. Furthermore, a greater mean total body clearance of R(+)- than of S(−)-bupivacaine (R:S ratio = 1.65) has been found after bolus administration of the individual enantiomers to sheep, in accord with a greater hepatic extraction of the R(+)- enantiomer [1].

Although it is essential to understand the intrinsic pharmacodynamic and pharmacokinetic profiles of each enantiomer, the situation becomes more complicated after administration of the racemate, when essentially two drugs are administered simultaneously—a situation which may potentiate or modulate the effects of each enantiomer [4]. In such situations, meaningful interpretation of pharmacokinetic data may be made only after enantioselective analysis because, unless this approach is taken, any difference in the

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time course of blood concentrations of the enantiomers may not be revealed [5]. With the exception of a study which reported on the enantiomers of prilocaine after administration of the racemate [6], there is no information, of which we are aware, regarding the fate of the enantiomers of the aminoacylaniline local anaesthetics after the racemate was given.

Information on bupivacaine (racemic) kinetics during prolonged administration remains contradictory: some studies have suggested no difference in kinetics with time [7, 8], whereas others have reported a decrease in clearance of bupivacaine with time [9, 10]. However, in all these studies, bupivacaine was assayed non-enantioselectively and, as Mazoit and colleagues [9] observed, a difference in the kinetic profile of the two enantiomers cannot be excluded as a cause.

Thus, because of the paucity of information in the anaesthesia literature regarding enantiomer kinetics of racemic (RS)-bupivacaine, the purpose of this study was two-fold; first, to determine the regional and total body clearances at steady state of R(+)- and S(−)-bupivacaine during the continuous i.v. infusion of RS-bupivacaine to subtoxic concentrations in conscious sheep, and second, to establish the kinetic profile over time. To achieve the latter, it was decided to continue the bupivacaine infusion to 24 h, at which time cardiovascular effects and regional kinetics of the two enantiomers were studied again and compared with those obtained at the earlier time.

MATERIALS AND METHODS

Institutional Ethics Review Committee approval was obtained. One study was performed in each of five sheep (mean weight 47 (SD 4) kg) prepared previously with chronic intravascular catheters to enable drug infusion, cardiovascular monitoring and regional blood sampling for blood flow indicator and R(+)- and S(−)-bupivacaine analyses. Each animal received a two-stage i.v. infusion of RS-bupivacaine to produce constant arterial drug concentrations. Urine samples during the 24-h period of infusion of bupivacaine and during the 24-h post-infusion period were obtained from each animal. All animals had free access to food and water throughout the study.

Animal preparation

A detailed description of the general methods and materials used for the animal preparation has been reported in previous publications from this laboratory [11, 12]; the methods specific to the present study are described here briefly. Under general anaesthesia, a left-sided thoracotomy was performed to ligate the hemi-azygos vein which, in the sheep, contributes systemic venous blood to the coronary sinus. Intra-abdominal catheters were placed directly into the abdominal aorta (distal to the renal artery and proximal to the iliac bifurcation), mesenteric and portal vein via left paravertebral and right subcostal skin incisions, respectively. After surgical exposure of the vessels in the neck, two arterial catheters were placed in the right carotid artery with their tips positioned approximately 2 cm above the aortic valve. Catheters were placed in the right jugular vein with their tips in the coronary sinus (CS), left renal vein, posterior vena cava (PVC), right hepatic vein and right atrium (two catheters), and a flow-directed thermodilution catheter was placed with its tip in the pulmonary artery (PA). An additional catheter was placed in the sagittal sinus (SS) via a frontal incision and a trephine hole in the parietal bone.

At least 1 week was allowed for the sheep to recover from surgery before the study was performed.

Baseline cardiovascular and blood flow measurements

Mean arterial pressure (MAP) was measured using an aneroid gauge connected via an extension line to one of the arterial catheters. Heart rate (HR) was measured at the same time as MAP, from the oscillation rate of a small bubble introduced into the extension line. Cardiac output (CO) was determined using the PA thermodilution catheter after injection of ice-cold saline 10 ml into a right atrial catheter.

Gut and hindquarter blood flows were measured by indicator dilution using infusion into the mesenteric vein and abdominal aorta, respectively, of the indicators sodium para-aminohippurate (PAH) and sodium bromsulphthalein (BSP). Liver and kidney blood flows were measured at times similar to those for gut and hindquarter blood flow by the Fick method using BSP and PAH, respectively. Steady-state blood concentrations of the indicators were achieved with two-stage infusions using a constant rate, two-channel infusion pump with calibrated glass syringes: a 15-min loading dose of BSP and PAH (respectively, 32 and 8 mg min^{-1}) was followed by a maintenance infusion (respectively, 16 and 4 mg min^{-1}). After 45 min of maintenance infusion, simultaneous ascending aortic and appropriate regional venous blood sample sets (0.4 ml) were drawn at 10-min intervals for a further 40 min. At the same times, MAP, HR, arterial pH and blood-gas tensions measurements were made simultaneously. These were termed "baseline" measurements.

Gut and hindquarter blood flows were calculated from the quotients, respectively, of the PAH and BSP maintenance dose rates and the appropriate venous–arterial concentration differences at steady state. Liver and kidney blood flows were calculated from the quotients, respectively, of the BSP and PAH maintenance dose rates and the appropriate regional arterial–venous concentration differences, at steady state.

Bupivacaine administration

After baseline cardiovascular and regional blood flow measurements were made, constant blood R(+)- and S(−)-bupivacaine concentrations were achieved with a two-stage infusion of RS-bupivacaine (as the hydrochloride salt) into a right atrial catheter. Loading doses of 4 mg min^{-1} for 15 min were followed immediately by maintenance doses of 1 mg min^{-1} to 24 h. This produced blood concentrations of RS-bupivacaine similar to those which might be achieved during continuous extradural analgesia [13]. To preclude any changes which might be caused by diurnal variation, all studies were commenced at 10:30.

Two time periods (3–4 h and 23–24 h) during the maintenance infusion were regarded as "steady-state" periods. During these periods, simultaneous blood samples (1.0 ml, individually weighed) were obtained at 20-min intervals from the aortic, PA, SS, CS, hepatic, portal, renal and PVC catheters for measurement of blood concentrations of R(+)- and S(−)-bupivacaine. During these steady-state periods MAP, HR, arterial pH and blood-gas tensions were obtained, together with CO and liver, kidney, gut and hindquarter blood flows, by methods described above.

Pharmacokinetic analysis

The total body clearances of the enantiomers of bupivacaine were obtained from the ratio of the maintenance infusion rate of racemate divided by 2 and the corresponding mean arterial concentration of enantiomer during each steady-state period. The regional clearances of the enantiomers were determined from the relevant products of the regional enantiomer extraction ratios and regional blood flows. The results of the indicator dilution measurement of gut blood flow were considered to be unreliable because of apparent streaming of the PAH. Gut flow was taken therefore as 80% of liver blood flow [11, 14] and the splanchnic component of hepatosplanchnic clearance was estimated from the product of the arterial–portal venous bupivacaine enantiomer extraction ratio and the estimated gut blood flow.

R(+)- and S(−)-bupivacaine concentrations

The enantiomers in blood were measured using a modification of the method of Lee, Ang and Lee [15]. To 1.0 ml of blood was added an internal standard (lignocaine 0.1 µg) and sodium hydroxide (200 µl of a 0.1-mol $litre^{-1}$ solution). The blood was extracted with n-hexane (HPLC grade) 5 ml by rotary mixing (10 min, 20 r.p.m.). The hexane layer was back-extracted with dilute phosphoric acid (200 µl of a 0.005-mol $litre^{-1}$ solution) by vortex mixing (1 min). After centrifugation (5 min, 4000 *g*), the hexane layer was discarded and the acid layer heated in a water bath (10 min, 70 °C) to remove residual hexane. A 40-µl aliquot of the acid solution was injected onto the HPLC column. Chromatography was performed using a 4 × 100-mm Enantiopac column (Pharmacia LKB, Biotechnology AB, Bromma, Sweden) with a mobile phase (sodium phosphate 0.01 mol $litre^{-1}$: 2-propanol, 94 : 6) at pH 7.0 using a flow rate of 0.3 ml min^{-1}. The u.v. detector was set at 214 nm, and the chromatogram recorded on a dual pen recorder. Up to approximately 600 samples were resolved successfully using this particular column, after which the packing collapsed. This was indicated by an increase in head pressure with consequent peak broadening. Standard curves were prepared for each enantiomer using RS-bupivacaine in blank blood over the range 0.1–1.0 mg $litre^{-1}$. Regression coefficients for each curve were generally 0.999 and the regression line essentially passed through the origin. In the range 0.1–1 mg $litre^{-1}$, the coefficients of variation were 5.0 and 5.9% for R(+)- and S(−)-bupivacaine, respectively ($n = 30$). The enantiomers in urine were measured in a similar manner after the urine had first been acidified and pre-extracted with ether to remove interfering substances appearing as peaks in the chromatograms.

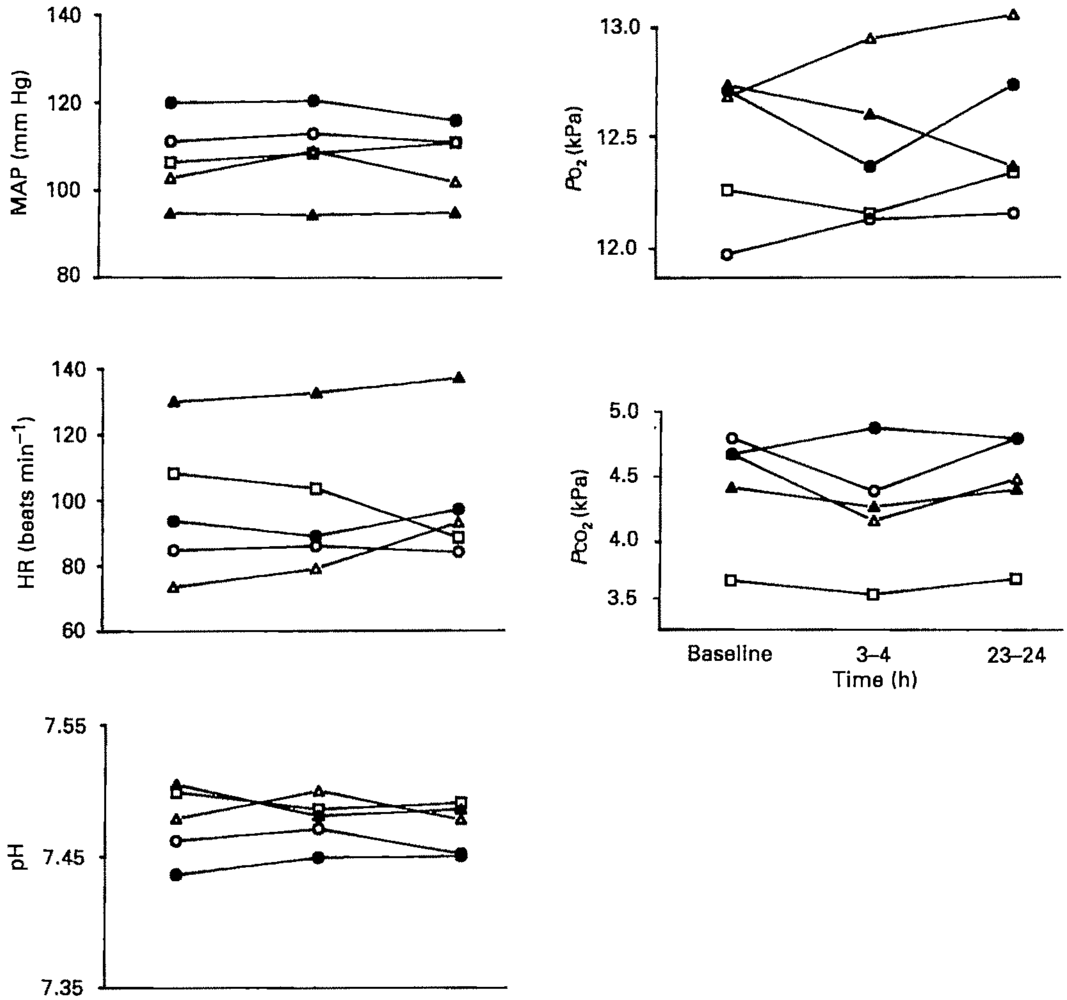

FIG. 1. Comparison of mean arterial pressure (MAP), heart rate (HR), arterial blood pH and gas tensions (Po_2, Pco_2) before (baseline) and during the 3–4 h and 23–24 h periods of infusion of bupivacaine (mean values for each period) in individual sheep, Nos 1 (○), 2 (●), 3 (△), 4 (▲) and 5 (□).

Statistical analysis

Regional extraction ratios and clearances during both periods were examined by the one-sample *t* test to determine if they were significantly different from zero. Overall drug effects on blood flow compared with baseline values were analysed by one-factor analysis of variance with repeated measures. Differences in arterial blood concentrations of enantiomers, extraction ratios and clearances for enantiomers at the 3–4 h and 23–24 h time periods were assessed by repeated measures analysis of variance. For all tests, $P \leqslant 0.05$ was considered significant.

RESULTS

Cardiovascular and blood flow measurements

With the exception of a slight decrease in cardiac output and liver blood flow (respectively, $P = 0.03$ and $P = 0.01$), administration of bupivacaine did not affect other cardiovascular variables (figs 1, 2).

Bupivacaine enantiomer kinetics

The resultant arterial blood concentrations of R(+)- and S(−)-bupivacaine for each animal over the 24-h time period are shown in figure 3:

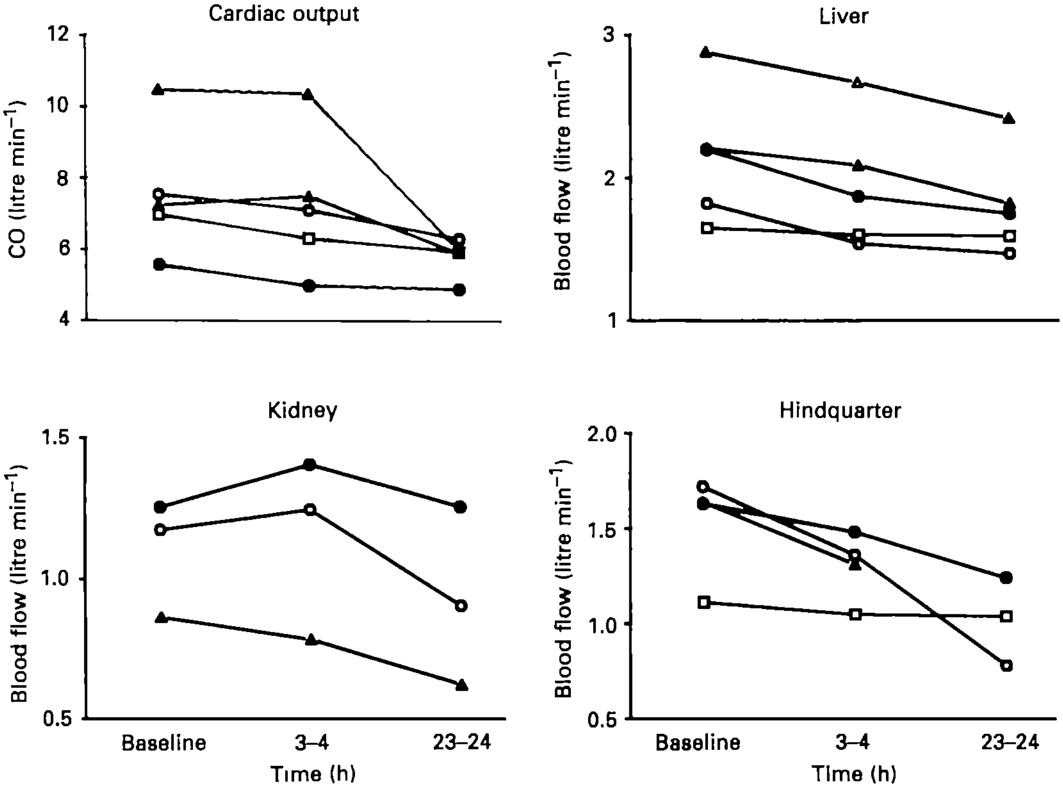

FIG. 2. Comparison of cardiac output, liver, kidney and hindquarter blood flow before (baseline) and during the 3–4 h and 23–24 h periods of infusion of bupivacaine (mean values for each period) in individual sheep, Nos 1 (○), 2 (●), 3 (△), 4 (▲) and 5 (□). With the exception of cardiac output ($P = 0.03$) and liver blood flow ($P = 0.01$), there were no significant differences in the respective values between the two periods. Kidney blood flow was not measured for sheep Nos 3 and 5. Hindquarter blood flow was not measured in sheep No. 4 and during the 23–24 h time period in sheep No. 3.

constant arterial blood concentrations occurred after about 2 h. In one animal (sheep No. 1), the blood samples were extracted using ether, which resulted in the chromatograms being uninterpretable after 13 h because of contamination of the peaks by (presumed) metabolites that had retention times similar to those of the parent enantiomers. The use of hexane as the extraction solvent with subsequent extractions overcame this problem. Thus results for the 23–24 h time period was obtained for four animals only.

Mean (SD) arterial concentrations of R(+)- and S(−)-bupivacaine at 3–4 h were not significantly different from those at 23–24 h ($P = 0.64$); however, the concentrations of R(+)-bupivacaine were significantly smaller than those of S(−)-bupivacaine ($P = 0.05$) (table I).

With the exception of the liver, the arterial–regional venous concentration gradients were not significantly different to zero. Mean regional extraction ratios of the enantiomers during both steady-state periods (3–4 h and 23–24 h), together with the 95% confidence interval, are presented in figure 4. During each period, bupivacaine was extracted significantly by the liver: mean (SD) ratios for R(+)-bupivacaine 0.69 (0.21) and 0.77 (0.19), respectively, and for S(−)-bupivacaine 0.54 (0.24) and 0.68 (0.15), respectively. Repeated measures analysis of variance showed that, within sheep, there was no difference in extraction ratio between the two time periods for each enantiomer ($P = 0.22$). However, there was a significant difference between the R(+)- and S(−)-enantiomer extraction ratios at both time periods ($P = 0.009$).

The corresponding mean (SD) clearances (*Cl*) of R(+)-bupivacaine by the liver were, respectively, 1.37 (0.57) and 1.47 (0.50) litre min^{-1}; and for

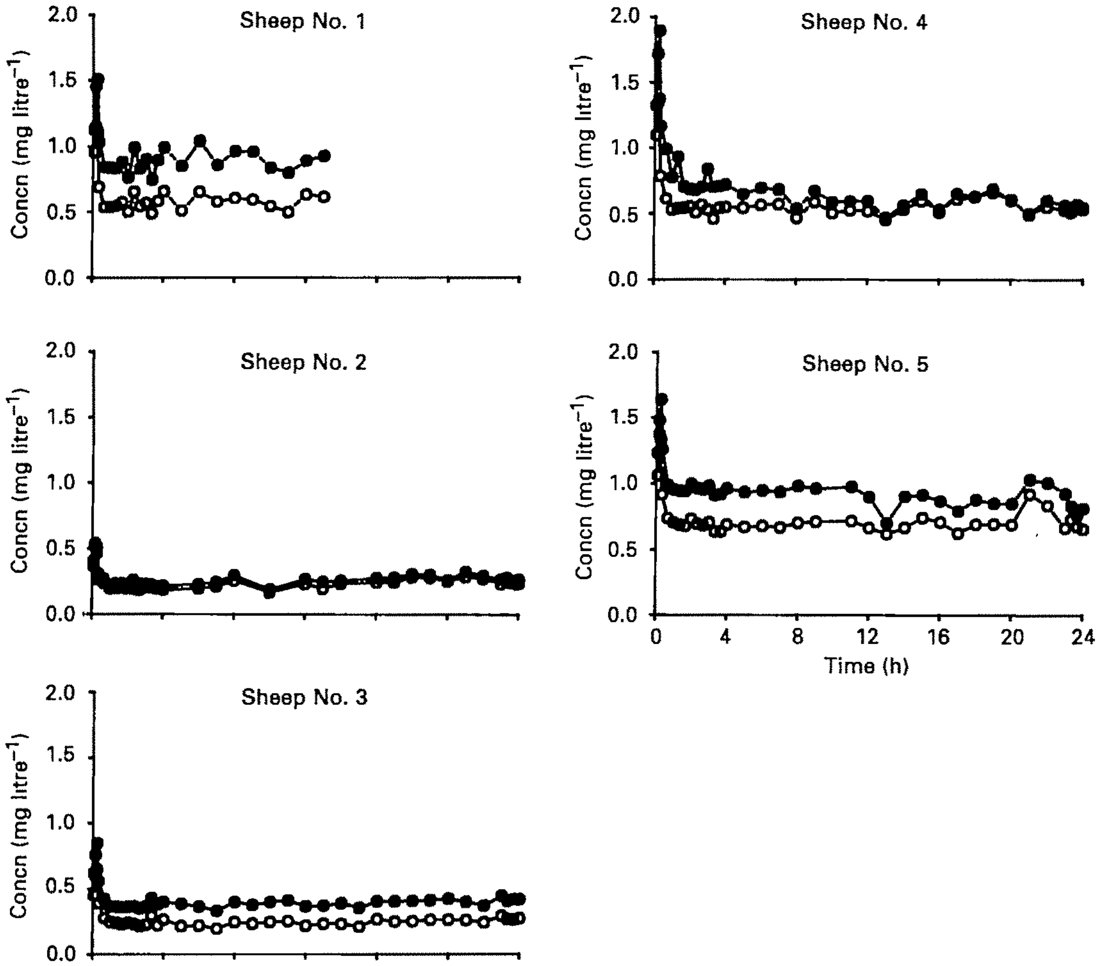

FIG. 3. Arterial blood concentrations of bupivacaine enantiomers during the infusion period. ○ = R(+)-Bupivacaine; ● = S(−)-bupivacaine. Because of contamination of HPLC peaks by metabolites, no data were obtained for sheep No. 1 after 13 h.

TABLE I. *Mean (SD) arterial blood concentrations of bupivacaine enantiomers at 3–4 h and 23–24 h. NA = Not available*

Sheep No.	3–4 h			23–24 h		
	R(+)-	S(−)-	R:S Ratio	R(+)-	S(−)-	R:S Ratio
1	0.58 (0.07)	0.88 (0.10)	0.66	NA	NA	NA
2	0.20 (0.01)	0.22 (0.01)	0.91	0.24 (0.01)	0.27 (0.01)	0.89
3	0.25 (0.03)	0.39 (0.03)	0.64	0.28 (0.01)	0.42 (0.02)	0.67
4	0.52 (0.04)	0.75 (0.06)	0.69	0.53 (0.01)	0.54 (0.03)	0.99
5	0.66 (0.04)	0.94 (0.03)	0.70	0.68 (0.03)	0.83 (0.07)	0.82

S(−)-bupivacaine, respectively, 1.01 (0.54) and 1.30 (0.33) litre min^{-1}. Mean clearances, together with the 95% confidence interval, of the enantiomers by the lung, liver, gut, kidney and hindquarters and *Cl* values derived by summation of individual regional clearances (Cl_{sum}) and from the ratio of the dose rate to the arterial blood concentration of enantiomer (Cl_{calc}) are shown in

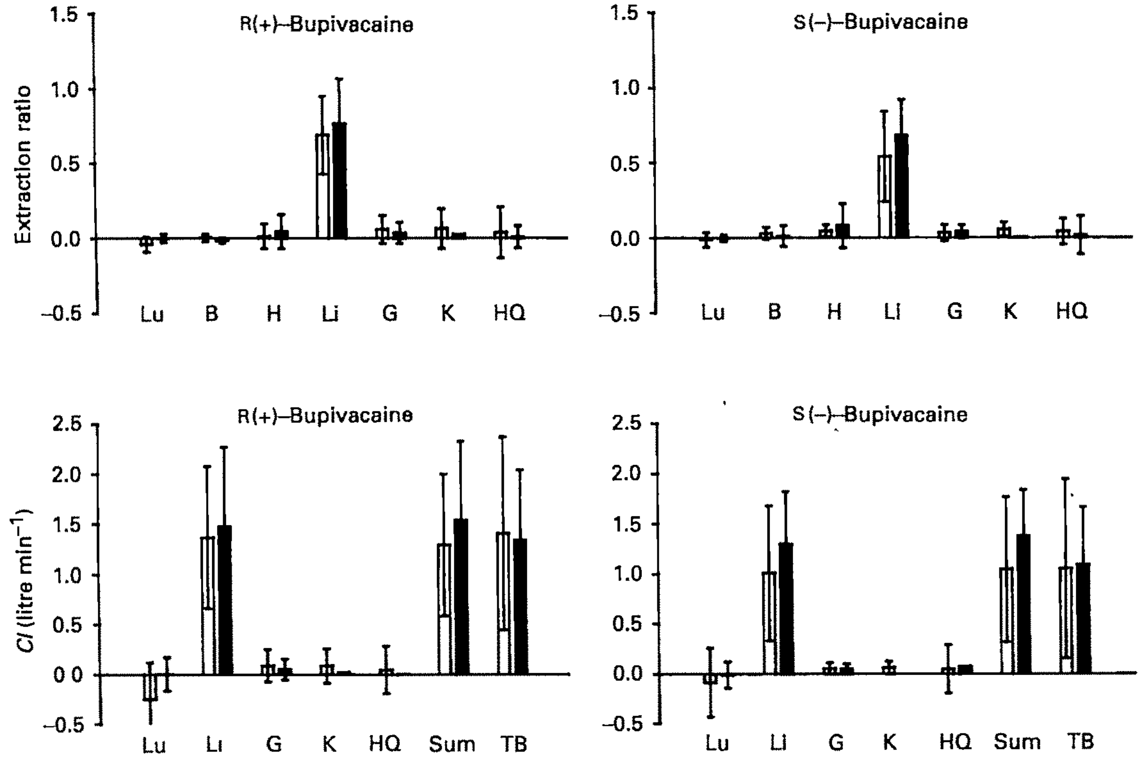

FIG. 4. Regional extraction ratios (top panel) and clearances (*Cl*) (lower panel) of R(+)- and S(−)-bupivacaine during the 3–4 h (□) and 23–24 h (■) periods of infusion of bupivacaine (population means and 95 % confidence interval). B = Brain; G = gut; H = heart; HQ = hindquarter; K = kidney; Li = liver; Lu = lung; TB = total body.

TABLE II. *Analysis of variance table: clearance. Effects of enantiomer (R(+)- vs S(−)-), time (3–4 h vs 23–24 h) and method of calculating clearance of bupivacaine were assessed by a three-factor analysis of variance with repeated measures of all factors. The two enantiomers were cleared at significantly different rates; clearance was independent of the time of measurement and method of measurement. No two-factor interactions were significant; the three-factor interaction was not included in the model*

Source	Sums of squares	Degrees of freedom	Mean square	*F*	*P*
Main effects					
Enantiomer	63.20	1	63.20	11.65	0.04
Enantiomer × sheep	16.28	3	5.43		
Time	0.07	1	0.07	0.01	0.91
Time × sheep	14.50	3	5.83		
Method	1.00	1	1.00	0.03	0.87
Method × sheep	99.53	3	33.18		
Two-factor interactions					
Enantiomer × time	4.00	1	4.00	2.38	0.22
Enantiomer × time × sheep	5.04	3	1.68		
Enantiomer × method	0.34	1	0.34	0.16	0.72
Enantiomer × method × sheep	6.48	3	2.16		
Time × method	7.50	1	7.50	1.64	0.29
Time × method × sheep	13.72	3	4.57		

figure 4. During the two time periods, mean Cl_{calc} values of R(+)-bupivacaine were 1.41, 1.34, respectively; those for S(−)-bupivacaine were 1.05 and 1.09, respectively. R:S ratios were 1.34 and 1.23. Repeated measures analysis of variance indicated that there was no significant difference within sheep between Cl_{sum} and Cl_{calc} ($P = 0.67$). The same test (table II) also indicated no within-sheep difference between liver clearance and Cl_{calc} ($P = 0.87$).

Analysis of urine showed that only one of the five sheep excreted measurable amounts of unmetabolized R(+)- and S(−)-bupivacaine in urine collected during the 24-h infusion period and in that collected during the 24-h post-infusion period. This amounted to, respectively, 0.96% and 0.35% (R(+)-bupivacaine) and 0.11% and 0.03% (S(−)-bupivacaine) of total enantiomer dose. There was no measurable amount of each enantiomer in the urine collected from the other sheep. Accordingly, there was no significant clearance of R(+)- and S(−)-bupivacaine by the kidney.

DISCUSSION

Reporting of pharmacokinetic and pharmacodymamic studies of racemic drugs has recently been debated vigorously [5, 16]. The reason for this is that more than 60% of clinically-useful drugs are marketed as racemic mixtures [5], and yet the vast majority of drug assay data continue to be presented as if only one compound was involved. In fact, Ariëns [16] has gone as far as to say that "the neglect of stereochemical aspects has degraded many pharmacokinetic studies to expensive highly sophisticated psuedoscientific nonsense". This statement should, however, be tempered by adding that it has only recently become possible, through improved technology, to analyse biological fluids enantioselectively.

I.v. infusion of RS-bupivacaine 1 mg min^{-1} produced mean arterial blood concentrations at steady state which ranged from 0.20 to 0.68 mg litre^{-1} for R(+)-bupivacaine and from 0.22 to 0.94 mg litre^{-1} for S(−)-bupivacaine (table I). Furthermore, there was no tendency for convergence of blood concentrations of the enantiomers (fig. 3), thus confirming a previous finding [1] that there is no evidence of enantiomer inversion of bupivacaine *in vivo* as a metabolic pathway. Metabolic clearance of this type has been shown, for example, for some non-steroidal anti-inflammatory drugs [17]. These concentrations, corresponding to a range of RS-bupivacaine 0.42–1.60 mg litre^{-1}, produced no notable effects on the cardiovascular variables measured. The slight decrease from baseline values in CO ($P = 0.033$) was influenced by the almost halving of its baseline and 3–4 h time period values at the 23–24 h time period in sheep No. 4 (fig. 2). The reason for this remains unexplained; it was not associated with a decrease in liver blood flow of the same magnitude (fig. 2). During the infusion period there was a reduction in mean liver blood flow ($P = 0.01$). Furthermore, this decrease was gradual (mean baseline flow of 2.15 litre min^{-1}; mean flows of 1.95 litre min^{-1} at 3–4 h and 1.81 litre min^{-1} at 23–24 h) as there was a significant difference in liver blood flow at both the two time periods ($P = 0.046$, Student's paired *t* test). There are two possible explanations for the decrease in liver blood flow. First, that this may have been a characteristic of the animals adapting to being in the laboratory, or of a diurnal rhythm. Although placebo studies were not performed, the fact that each animal behaved similarly tends to suggest that the former is less likely. Second (a more likely explanation) is the net effect of administration of bupivacaine. This is in contrast to the report of Mazoit and colleagues [9] that prolonged infusion of bupivacaine in dogs caused no change in liver blood flow, and evidence that administration of lignocaine, bupivacaine or etidocaine produced increases in liver blood flow in humans [18, 19]. Administration of ropivacaine, an enantiomerically pure congener of mepivacaine and bupivacaine [20], in the dose range used, in a sheep preparation similar to that used in the present study, was found not to affect liver blood flow during infusion for 4 h [12]. As the clearance of these local anaesthetics is thought to parallel liver blood flow, a decrease in flow could produce, conceivably, a decrease in clearance. With the present study, the extraction ratios of the enantiomers (from mean (SD) of 0.54 (0.24) to 0.77 (0.19)), together with the overall decrease in liver blood flow (0.34 litre min^{-1}) has no effect on clearance. Thus our results suggest that the reduction in liver blood flow found in this study was of no importance.

Although extensive lung tissue uptake of racemic bupivacaine and other congeners has been shown to occur *in vitro* [21], experiments performed after brief infusions of bupivacaine in dogs [22] and prolonged i.v. infusions of lignocaine and ropivacaine in sheep [12, 23] continue to suggest that this lung uptake is caused by transient drug distribution rather than a metabolic or other clearance. As there was no pulmonary arterial to aortic gradient at both steady-state periods, it is concluded that the two enantiomers of bupivacaine were not cleared by the lungs.

Evidence of clearance of the enantiomers of bupivacaine by the brain and heart was not found and there was no clearance by the splanchnic region drained by the portal vein. This is in contrast with that which was noted after i.v. infusion of ropivacaine in sheep [12], when extraction occurred across the gut and which was postulated to be caused by ion-trapping of the conjugate acid. Although bupivacaine, with a pK_a similar to that of ropivacaine, would have been expected to undergo a similar distribution, results of the present study indicated no net extraction by the gut of each enantiomer at both steady-state time periods.

Clearance by the kidneys of aminoacylaniline local anaesthetics in humans is uniformly small, with mean fractions of 0.01–0.03 excreted unmetabolized into urine [24]. Only one sheep had detectable amounts of each enantiomer in the urine, being less than 1 % of the dose and with an R:S ratio of 10:1, indicating stereoselectivity. Overall, clearance of bupivacaine by the kidneys observed in this study by both direct measurement and by urinary excretion, indicated that this was a negligible site for clearance.

There was no evidence of extraction of either enantiomer by the hindquarters. This is in contrast with other findings for this laboratory [25] in spinally anaesthetized sheep, of evidence of extraction of racemic bupivacaine by the hindquarters. With that study, bupivacaine was infused i.v. for 3 h but, because there was no initial loading dose, distribution steady state (at which arterial and venous concentrations are similar) was not achieved. Prolonged distribution into fat and muscle, therefore, was manifested as a positive extraction ratio.

Unlike ropivacaine, for which 85 % of clearance was attributed to that by the liver [12], the present study indicated that the clearance of each enantiomer was accounted for exclusively by liver clearance. Furthermore, there was no evidence that tissue uptake and distribution of each enantiomer was still taking place, as *Cl* derived by the summation of all regions (Cl_{sum}) was similar to that derived by the quotient of the dose and arterial blood drug concentration (Cl_{calc}). *Cl* for R(+)-bupivacaine was always greater than that for the S(−)- form (R:S ratio 1.34 at 3–4 h and 1.23 at 23–24 h). This ratio is somewhat less than the value of 1.65, reported after administration of the single enantiomer [1] which does not allow for possible enantiomer interaction. The difference between the studies of administration of enantiomers separately and as racemate therefore could indicate that the R(+)- enantiomer inhibits partially the clearance of its antipode.

Conflicting reports on the pharmacokinetics after administration of racemic bupivacaine exist in the literature [7–10]; in particular, it has been suggested that extrapolation of pharmacokinetic data obtained after a short to prolonged i.v. infusion of bupivacaine in dogs should be made with care, in that an increase in the terminal half-life and decrease in *Cl* was observed with time [9]. The significance of this lies in the potential for drug accumulation and hence, risk of toxicity. To eliminate the complications introduced by experimental designs which favour perfusion-limiting or diffusion-limiting pharmacokinetics which might be found after a short i.v. infusion (non-steady state) followed by a prolonged i.v. infusion of bupivacaine (steady state), the design of our study differed from others in that the pharmacokinetic parameters were obtained during two steady-state time periods. Findings of the present study have indicated that, although a difference in *Cl* values exists between the enantiomers of bupivacaine, no difference was found between the two time periods.

In summary, we have found that, after i.v. administration of racemic bupivacaine at 1 mg min^{-1} there were different time courses of clearance of the enantiomers. Both enantiomers were cleared by the sheep liver exclusively with R(+)-bupivacaine being cleared more rapidly than S(−)-bupivacaine; after steady state was reached, the value of *Cl* of each enantiomer was not altered by prolonged infusion. It is fortunate that *Cl* of the R(+)- enantiomer is greater than that of the S(−)- form, as the R(+)- enantiomer has been shown to be significantly more toxic than its antipode [13, 26]. The pharmacokinetics in the sheep appears to predict the outcome in humans quite well: the mean R:S ratio of blood concentrations of bupivacaine in the present study is similar to that (0.72 (SD 0.11)) found in 184 blood samples from 13 patients undergoing repeated intercostal nerve blocks [27].

ACKNOWLEDGEMENTS

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INHALATION INDUCTION OF ANAESTHESIA WITH ISOFLURANE: EFFECT OF ADDED CARBON DIOXIDE

S. A. COLEMAN, J. W. McCRORY, C. J. VALLIS AND R. J. BOYS

SUMMARY

Fifty children underwent inhalation induction of anaesthesia with isoflurane and nitrous oxide in oxygen with or without the addition of 5% carbon dioxide. Addition of carbon dioxide resulted in more rapid induction and significantly reduced the incidence and severity of airway related problems.

KEY WORDS

Anaesthesia: paediatric. Anaesthetic techniques: inhalation induction. Anaesthetics, volatile: isoflurane.

Inhalation induction of anaesthesia is a popular technique in paediatric practice. Halothane is a safe agent with a low incidence of side effects, even after repeated use. Isoflurane has the advantages of lower blood solubility and fewer adverse cardiovascular effects [1]. Its metabolism is minimal and this may reduce the potential for organ toxicity following repeated exposure. However, the irritant effect of isoflurane on the airway may cause respiratory complications which prolong induction and produce significant reductions in oxygen saturation in up to 50% of children [2, 3]. Premedication may reduce, but does not eliminate, these complications [4–6].

Addition of carbon dioxide to inspired gases stimulates ventilation and may reduce the incidence of breath-holding and laryngospasm. Unlike halothane, isoflurane has not been shown to potentiate cardiac arrhythmias in the presence of hypercapnia [1, 7–9]. This study was designed to assess the effect of addition of 5% carbon dioxide to inspired gases during inhalation induction of anaesthesia with isoflurane.

PATIENTS AND METHODS

Approval of the District Ethics Committee and informed parental consent were obtained for the study.

Following i.m. premedication with atropine 0.015 mg kg^{-1}, 50 children (ASA I, weight 4–15 kg) were allocated randomly to one of two groups: group A ($n = 25$) received inhalation induction of anaesthesia with isoflurane and nitrous oxide in 30% oxygen; group B ($n = 25$) received the same anaesthetic mixture, but with the addition of 5% inspired carbon dioxide. Fresh gas flows of 10 litre min^{-1} were administered via facemask and Ayre's T-piece, with Jackson–Rees modification. The inspired isoflurane concentration was increased by 0.5% increments, as tolerated clinically, to a maximum of 5%.

The anaesthetics were administered by one of two anaesthetists with limited previous experience of inhalation induction with isoflurane. Patients were monitored using continuous electrocardiography, digital pulse oximetry (Biox 3700) and capnography (Engstrom Erica). Capnograph sampling tubing was connected to a modified angle-piece which allowed sampling of expired gases to occur at the patients lips. An observer recorded heart rate, oxygen saturation (Sp_{O_2}) and percentage expired carbon dioxide at 30-s intervals, with additional recordings if Sp_{O_2} decreased to less than 85%. Times to onset of regular ventilation, insertion of oropharyngeal airway and attainment of 5% inspired isoflurane were noted. Coughing, breath-holding, laryngospasm, salivation or struggling were recorded, together with the smallest associated value of Sp_{O_2}. The anaesthetist was informed if Sp_{O_2} decreased to less than 85% and he was allowed to abandon the induction technique at any time if clinically indicated.

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Differences in continuous measurements between groups were assessed using Student's two-sample *t* test, with Welch's correction when variances were significantly different. When distributions were particularly skewed, a logarithmic transformation was performed before testing and hence geometric, rather than arithmetic, means are quoted. The 2 × 2 tables were analysed using Fisher's exact test.

The significance of factors affecting induction times was obtained by multiple linear regression and that of factors affecting complication rates, using a logistic model. In a logistic model, the log odds of a complication are related to a linear combination of the factors.

RESULTS

The groups were similar in age, weight and sex distribution (table I).

Time to attainment of 5 % inspired isoflurane was significantly shorter in patients breathing additional carbon dioxide (group B) (fig. 1) (mean time 3.1 min compared with 4.8 min; $P < 0.01$).

The number of patients with complications was significantly fewer in group B (8 % compared with 44 % in group A; $P < 0.05$) (table II). The number of instances of coughing, breath-holding and laryngospasm was reduced significantly in group B (table III). Salivation and struggling were also less frequent in group B, but these incidences were not significantly different. Cardiac arrhythmia was not detected in any child and mean maximum heart rates were similar in both groups.

Mean maximum expired carbon dioxide in group A was 5.4 % (range 3.9–9.0 %), compared with 7.6 % (range 5.5–9.0 %) in group B (fig. 2).

The incidence of complications was not related to age, weight or sex of the child. The incidence did not differ between the two anaesthetists, and no decrease in incidence or severity of complications was observed as the study progressed.

All 25 children in group B maintained $Sp_{O_2} >$ 85 %, compared with 21 children in group A (fig. 3). Cyanosis was detected in three children, all in group A.

TABLE I. *Patient data for the two groups (mean (range))*

	Without CO_2 ($n = 25$)	With CO_2 ($n = 25$)
Age (months)	15.1 (2–37)	15.0 (1–35)
Weight (kg)	10.1 (4–15)	9.8 (4.7–15)
Sex (M:F)	20:5	21:4

DISCUSSION

In previous studies of unpremedicated children, induction of anaesthesia with isoflurane was

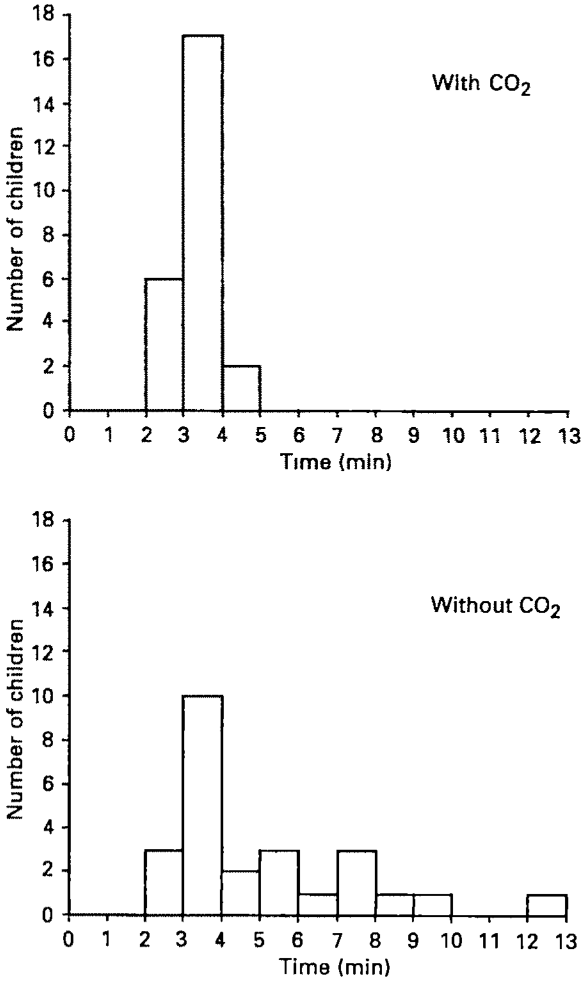

FIG. 1. Time to attainment of 5 % inspired isoflurane during induction of anaesthesia.

TABLE II. *Number of patients with complications during induction of anaesthesia with isoflurane with or without added carbon dioxide*

	Without CO_2 ($n = 25$)	With CO_2 ($n = 25$)	P
Complications	11	2	< 0.01
No complications	14	23	

TABLE III. *Number of complications during induction of anaesthesia with isoflurane with or without added carbon dioxide*

	Without CO_2 ($n = 25$)	With CO_2 ($n = 25$)	P
Cough	6	0	< 0.05
Breath-holding	8	0	< 0.005
Laryngospasm	11	2	< 0.01
Salivation	5	0	0.05
Struggling	5	1	ns
Arrhythmia	0	0	ns

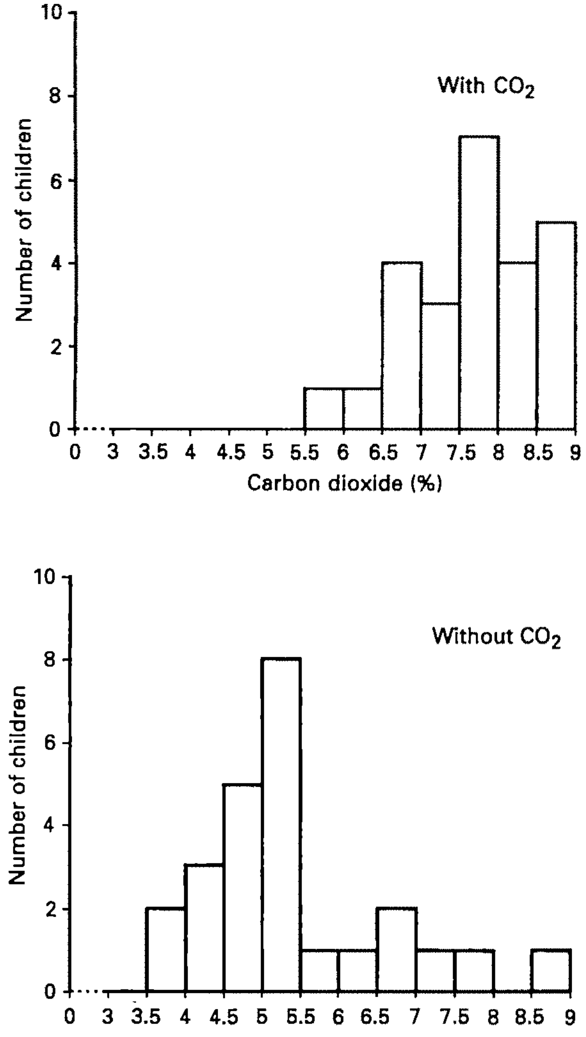

FIG. 2. Maximum expired carbon dioxide percentages during induction of anaesthesia.

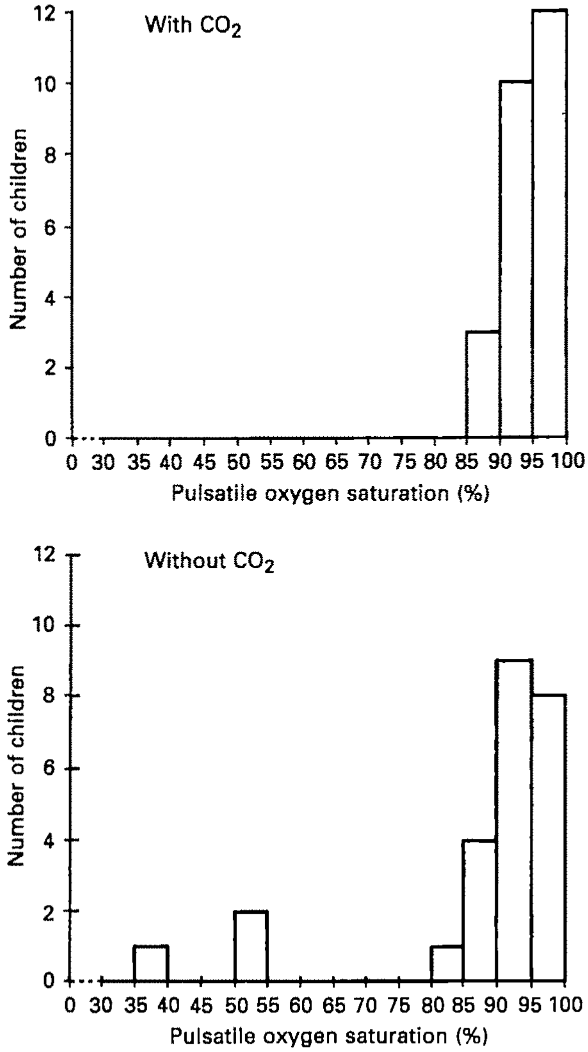

FIG. 3. Minimum oxygen saturations during induction of anaesthesia.

associated with an incidence of airway related complications of between 21 and 67% [10, 11]. Comparison of Sp_{O_2} in unpremedicated children during inhalation induction with isoflurane or halothane revealed significant desaturation in up to 50% of those receiving isoflurane [2, 3]. Sedative premedication may reduce the incidence of complications [6], but may prolong recovery—a particular disadvantage in children undergoing day-case surgery. Crean and colleagues found that premedication with atropine reduced significantly the incidence of airway complications, although desaturation occurred occasionally and induction time was not shortened [5]. Use of oxygen alone as the carrier gas would delay the onset of desaturation during respiratory complications, but this effect might be offset by prolongation of induction time and increased incidence of complications in the absence of nitrous oxide [7, 8]. Van Heerden and colleagues showed that humidification of the inspired gas mixture was associated with fewer complications during induction with isoflurane. However, there were insufficient children in their study for any firm conclusion to be made about the value of this technique in paediatric practice [12].

Addition of carbon dioxide to inspired gases in order to accelerate induction of anaesthesia has been practised for many years [13]. A recent survey of anaesthetists in the United Kingdom revealed that 13% of respondents currently use carbon dioxide for this purpose [14]. However, the technique is not without hazard. Halothane may cause cardiac arrhythmias in the presence of hypercapnia, but this has not been demonstrated with isoflurane [7, 8].

End-tidal carbon dioxide partial pressures of between 9.0 and 11.6 kPa have been recorded in children breathing isoflurane after sedative premedication, without arrhythmias [9]. With our sampling site, a small degree of mixing of expired gases was unavoidable, so true end-tidal concentrations of carbon dioxide may have been somewhat greater than those recorded. However, no cardiac arrhythmia was observed in any patient. Interestingly, a child in group A developed a peak expired concentration of carbon dioxide equal to the greatest value recorded in group B (9.0%). This occurred during an episode of breath-holding, coughing and laryngospasm and was accompanied by severe desaturation.

The more rapid attainment of 5% inspired isoflurane in group B was not unexpected. Of greater importance was the marked reduction in the incidence and severity of complications when 5% carbon dioxide was added to the inspired mixture. Complications occurred in 8% of patients in group B—an incidence similar to that reported by other workers studying inhalation induction with halothane [2, 3, 10, 11]. The complications were minor, required no alteration in anaesthetic technique and were not associated with any change in Sp_{O_2}, which remained greater than 85% in all children in group B. Sp_{O_2} values between 85 and 90% were recorded in three infants in group B, all in association with crying on arrival in the anaesthetic room. In each case, Sp_{O_2} increased rapidly with administration of the anaesthetic and cessation of crying.

Arterial saturation values less than 85% occurred only in group A ($n = 4$) and were always associated with respiratory complications.

We conclude that, in small children, airway related complications may be common during inhalation induction with isoflurane and nitrous oxide and are not prevented by premedication with atropine. Addition of 5% carbon dioxide to the inspired gases significantly reduced the frequency and severity of these complications and provided a quality of induction similar to that achieved normally with halothane. The availability of carbon dioxide on the anaesthetic machine is not, of course, without potential hazard; however, with flow-limited carbon dioxide rotameters and adequate monitoring, we believe this is a safe technique.

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MENTAL FUNCTION AFTER GENERAL ANAESTHESIA FOR TRANSURETHRAL PROCEDURES

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SUMMARY

We have assessed the influence of age and preoperative mental status score on postoperative mental function, using a choice reaction time test. One hundred and twelve patients (mean age 70 yr, range 48–88 yr) were given a standardized general anaesthetic for transurethral procedures. Mental status before anaesthesia was measured with the Clifton Assessment Procedure for the Elderly (CAPE). Reaction time was measured before anaesthesia and for up to 3 days after anaesthesia. Variability in reaction time performance was increased 24 h after anaesthesia in transurethral patients, but not in a control group of orthopaedic patients ($P = 0.0006$*). Factors contributing to increased variability of reaction time after operation in a multiple regression analysis were reduced CAPE score before operation (*$P < 0.0001$*), extent of surgery (*$P = 0.023$*), postoperative pain (*$P = 0.007$*) and postoperative sedative drugs (*$P = 0.009$*). Factors not contributing included age, diagnosis of cancer, number of previous operations in past 5 years, duration of anaesthesia, minimum mean arterial pressure, minimum and maximum perioperative* $P\text{CO}_2$ *values, postoperative pyrexia and poor sleep.*

KEY WORDS

Anaesthesia: general. Psychological responses: postoperative mental status, postoperative reaction time.

Transient mental impairment after anaesthesia has been reported in all surgical patients, which increases the burden of care [1–5]. Although clinical observation indicates that elderly patients suffer from relatively more transient mental impairment, studies have revealed inconsistent findings [5–8]. It has been reported that deficits in orientation and concentration occurred 2 days after anaesthesia in a group of patients of mean age 69 yr, but not in a younger group (mean age 50 yr) [6]. In contrast, other studies have found no correlation between age and postoperative mental function measured in several ways [7, 8]. However, all these studies have been deficient in some respects.

We have reported previously preliminary results in elderly patients undergoing transurethral surgery with standardized anaesthesia which suggested that a low score on a mental status test, rather than chronological age before operation, predisposes to postoperative mental impairment [9]. We now report the results of a larger study. Mental function was assessed for up to 3 days after operation using a reaction time test shown previously to be sensitive to the effects of anaesthesia for up to 2 days after operation in middle-aged patients [10]. The study was designed to observe if age, preoperative mental impairment and other risk factors predispose to postoperative mental impairment measured by reaction time. Confounding clinical factors were measured and reaction time measurements were made also in a small control group of hospital patients who had not recently had an operation.

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PATIENTS AND METHODS

The study was approved by the Ethics Committee of the local district health authority. We studied 112 patients of mean age 70 yr (range 48–88 yr), undergoing endoscopic urological procedures (table I). Patients who, in the opinion of the anaesthetist, required spinal anaesthesia were excluded. Patients were premedicated with temazepam 20 mg by mouth 1 h before operation. Anaesthesia was induced with thiopentone and maintained with nitrous oxide and halothane or enflurane in oxygen. We intended originally that all patients in the study should receive halothane, but decided to change to enflurane after 14 patients had been studied, after further concern about halothane and liver damage [11]. Alcuronium was used for neuromuscular block for procedures expected to last longer than 20 min; otherwise the patients breathed spontaneously.

On the day before surgery, patients were screened using the Information–Orientation subscale of the Clifton Assessment Procedure for the Elderly (CAPE) [12]. This 12-item mental status test was used to screen for a subgroup of elderly patients with possible preoperative mental impairment. In addition, patients were asked to rate any pain or discomfort and quality of previous night's sleep on a fixed-point scale. The research nurse who carried out all performance testing and recording of other variables throughout the study also noted any signs of confused behaviour, particularly in relation to understanding the instructions on a visual four-choice reaction time test which was used to assess postoperative recovery objectively. In this task, run by a BBC B computer, reaction time was separated from motor time. Twelve practice trials were given, followed by two blocks of 40 trials and the reaction time data were stored on disc. Subsequently, the computer printed a record of all individual trials and calculated a mean, median and SD score from 70 responses, ignoring the first five trials in each block. Reaction time was re-tested 1, 2 and 3 days after anaesthesia, or until the patient was discharged: all 112 patients were tested 24 h after anaesthesia; most patients undergoing only investigation or minor surgical procedures were then discharged.

TABLE I. *Demographic details and preoperative score on the Clifton Assessment Procedure for the Elderly (CAPE) for patients and controls*

	Transurethral patients (n = 112)	Hospital controls (n = 26)	Ambulant controls (n = 10)
Age (yr) (mean (SD))	70.5 (9.7)	64.5 (16.6)	75.3 (6.7)
Sex (M/F)	105/7	11/15	8/2
CAPE score (maximum = 12)			
12	88	22	8
11	18	2	1
10	4	1	1
9	2	1	0

Extent of surgery was scored: 1 = investigation only; 2 = bladder biopsy, resection of small bladder tumours and miscellaneous procedures; 3 = resection of large bladder tumours and prostates.

Twenty-six orthopaedic patients (mean age 64 yr) at least 12 days post-surgery served as controls (table I); they also were screened with the CAPE and had subjective assessments and reaction time tested at the same days and times of day. It was difficult to study elderly control hospital patients who had not recently had an operation or were comparable in physical fitness to the patients undergoing transurethral procedures. Therefore 10 ambulant elderly volunteers, of mean age 75 yr, from a local social club for the elderly also were screened with the CAPE and tested twice, once to act as a baseline and again to correspond to 1 day after anaesthesia (table I).

The following variables were recorded during anaesthesia: arterial pressure and heart rate at 1-min intervals; duration of anaesthesia, defined as time from induction to discontinuation of nitrous oxide; anaesthetic incidents, e.g. hypotension; bladder irrigation during surgery.

In 78 patients, arterialized venous $P\text{CO}_2$ was measured before and during anaesthesia at 15-min intervals with a Radiometer ABL 3 blood-gas analyser [13]. This was not performed on a random sample of patients, but was undertaken if there was sufficient time available in the operating theatre.

Statistical analysis

Independent t tests were used to test if transurethral and control groups were comparable in age and baseline reaction time score. Reaction time performance after anaesthesia was very variable in the transurethral group. Therefore change in reaction time performances from baseline to after anaesthesia was examined within this

TABLE II. *Measurements made before, during and after anaesthesia in 112 patients undergoing transurethral procedures (mean (SD), or number)*

Weight (kg) ($n = 106$)	71.1 (12.4)
Duration of anaesthesia (min) ($n = 110$)	30.9 (20.3)
Mean arterial pressure before anaesthesia (mm Hg) ($n = 106$)	98.2 (21.2)
Minimum mean arterial pressure during anaesthesia (mm Hg) ($n = 106$)	75.8 (16.5)
Minimum arteriovenous P_{CO_2} (kPa) ($n = 78$)	5.4 (1.3)
Maximum arteriovenous P_{CO_2} (kPa) ($n = 78$)	5.7 (1.5)
Patients receiving halothane (No.)	14
Patients receiving enflurane (No.)	98

group and the small control group using Friedman non-parametric analysis of variance followed by Wilcoxon matched pairs tests. Mann–Whitney *U* tests were used also to test for differences in reaction time performance between groups. Multiple regression was carried out on change in SD of reaction time score using the multiple regression and best subset regression program from the BMDP statistical package [14].

(The computer program for the reaction time test and data analysis are available on request at a small charge.)

RESULTS

Preoperative CAPE scores for transurethral patients and orthopaedic controls are shown in table I, and other measurements made before, during and after anaesthesia are given in table II. On the basis of hospital records and patient reports, 46% of transurethral patients with reduced CAPE scores had evidence of cardiovascular disease, compared with 34% of maximally scoring patients (chi-square test, $P = 0.4$). Seven patients acted as subjects twice, as they required repeat operations within the study, and five patients received non-standard anaesthesia. The data were analysed both retaining and excluding these subjects.

An independent *t* test (using the appropriate separate estimates of variance, as there was a significant difference in variance between the groups, Levene *F* for variances $P = 0.0002$), carried out on the ages of transurethral patients and orthopaedic patient controls, indicated no significant difference in mean age. In addition to age being more variable, there was a greater proportion of females in the control group (table I). However, independent *t* tests showed there was no significant difference between transurethral patients and controls in baseline reaction time measured by median score ($P = 0.28$) or SD score ($P = 0.98$) (table III).

Fifty-seven and 35 patients, respectively, were available for testing 2 and 3 days after anaesthesia (table IV). Inspection of individual trials of reaction time together with means for the block of trials indicated that, when mean reaction time was increased after anaesthesia, this occurred not because each trial was longer, but because the frequency of particularly long responses was increased. Reaction times exceeding 1 s occurred and, in one patient, were frequent and persisted until the 3rd day after anaesthesia. Medians and SD of 70 reaction time trials are therefore presented [15] (table III). A Wilcoxon matched pairs signed rank test performed on the difference in median and SD of reaction time from baseline to 24 h after anaesthesia showed a statistically significant increase in the SD of reaction time scores in transurethral patients, but not in orthopaedic controls ($P = 0.0026$, $n = 112$; excluding repeat patients and patients receiving non-standard anaesthesia, $P = 0.0006$, $n = 100$). However, the same paired comparison of median reaction time was not significantly different in patients or orthopaedic controls, for either the total of 112 patients, or the 100 patients after exclusions. Comparison between transurethral patients and orthopaedic controls of difference from baseline reaction time scores using Mann–Whitney *U* tests showed no significant difference in SD ($P = 0.08$) or median scores. There was no significant difference in median reaction time or SD of reaction time between baseline and day 1 testing in the group of ambulant controls (table III). Only five patients undergoing transurethral procedures were rated as showing signs of confusion after anaesthesia. Inspection of reaction data indicated that only two of these also showed deficit in reaction time performance.

Friedman non-parametric analysis of variance was carried out on SD and median measures of reaction time for baseline and days 1, 2 and 3 after anaesthesia, in patients and orthopaedic controls for complete cases. Wilcoxon matched pairs tests were carried out comparing differences between day 1 and baseline, day 2 and baseline and day 3 and baseline. Again, there was a statistically significant increase in the SD of reaction time score between baseline and day 1 after anaesthesia for

TABLE III. *Mean* (SEM) *reaction time scores for median and* SD *of 70 trials in transurethral patients and hospital controls before and 1, 2 and 3 days after anaesthesia and in ambulant controls to correspond with 1 day after anaesthesia. **Significant difference between baseline and 1 day after anaesthesia* (P = *0.0026, Wilcoxon matched pairs test*); *other differences at this time ns*

	Reaction time (ms)			
	Baseline	Day 1	Day 2	Day 3
Median				
Transurethral patients	339 (5) (*n* = 112)	339 (5) (*n* = 112)	335 (7) (*n* = 57)	326 (10) (*n* = 35)
Hospital controls	345 (11) (*n* = 26)	342 (8) (*n* = 26)	325 (10) (*n* = 21)	319 (9) (*n* = 19)
Ambulant controls	362 (16) (*n* = 10)	349 (12) (*n* = 10)		
Standard deviation				
Transurethral patients	80 (9) (*n* = 112)	106 (13)** (*n* = 112)	79 (12) (*n* = 57)	75 (9) (*n* = 35)
Hospital controls	90 (19) (*n* = 26)	81 (14) (*n* = 26)	66 (7) (*n* = 21)	62 (9) (*n* = 19)
Ambulant controls	64 (8) (*n* = 10)	64 (8) (*n* = 10)		

TABLE IV. *Details of numbers of patients undergoing various types of transurethral procedures, and the days after anaesthesia on which they were tested*

Transurethral procedure (No. patients)	Day of test		
	1	2	3
Investigation	21	—	—
Resection prostate	40	39	26
Resection bladder tumour/biopsy	31	10	8
Miscellaneous (removal of bladder and ureteric calculi, urethrotomy)	20	8	1
Total	112	57	35

TABLE V. *Mean* (SEM) *reaction time scores for median of 70 trials for transurethral patients and hospital controls before and 1 and 2 days after anaesthesia.* **P = *0.01 compared with baseline* (*Wilcoxon matched pairs test*)

	Reaction time (ms)		
	Baseline	Day 1	Day 2
Transurethral patients (*n* = 57)	341 (7)	344 (8)	335 (7)
Hospital controls (*n* = 21)	351 (13)	338 (9)	328 (10)**

the 57 patients tested for 2 days after operation (Friedman Test Statistic = 22.99, $P = 0.00001$; Wilcoxon matched pairs test $P = 0.0001$) and the 35 patients tested 3 days after operation (Friedman Test Statistic = 16.97, $P = 0.007$; Wilcoxon matched pairs test $P = 0.0022$). There were no significant differences between day 2 and 3 performances for the SD measure, compared with baseline in either patients or orthopaedic controls. For the median measure of reaction time, there was a significant decrease in final day 3 performance compared with baseline in patients (Friedman Test Statistic = 11.9, $P = 0.01$; Wilcoxon matched pairs test $P = 0.0053$ ($n = 35$)) and orthopaedic controls (Friedman Test Statistic = 12.8, $P = 0.007$; Wilcoxon matched pairs test $P = 0.01$ ($n = 19$)). However, for day 2 performance this was significantly decreased from baseline only in orthopaedic controls (Friedman Test Statistic = 12.17, $P = 0.002$; Wilcoxon matched pairs test $P = 0.01$ ($n = 21$)). Median reaction time data for days 1 and 2 after anaesthesia are shown in table V.

Multiple regression and best subset regression were performed on change in SD of reaction time score 1 day after anaesthesia (fig. 1). This was carried out excluding patients tested twice, those having non-standard anaesthesia and the positive outlier of +1197. Factors contributing to increased variability of reaction time after operation were: reduced CAPE score before operation ($P < 0.0001$ (95% confidence interval (CI) = −93 to −34)); extent of surgery ($P = 0.023$ (95% CI = 3–48)); occurrence of pain after operation ($P = 0.007$ (95% CI = 14–87)) and administration of sedative drugs after operation ($P = 0.009$ (95% CI = 30–200)). The contribution of halothane

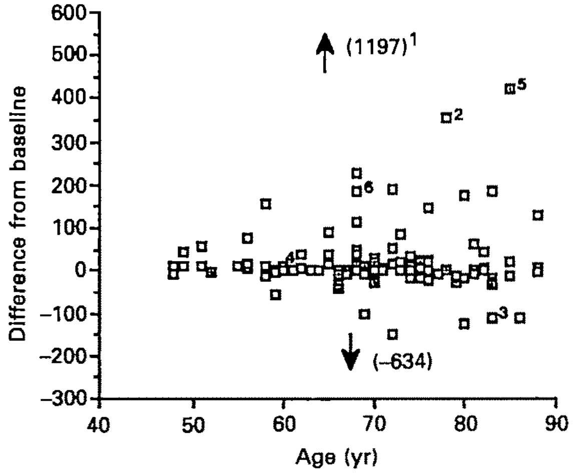

FIG. 1. Change from baseline in SD of reaction time score 1 day after anaesthesia, compared with age. Numbers 1–6 indicate patients with a psychiatric disorder, a history of stroke or having had an anaesthetic incident. Values in parentheses indicate the scores of outliers.

anaesthesia was also statistically significant ($P = 0.02$ (95% CI = −102 to −90)). However, as all the halothane cases were at the beginning of the series, a time dependent variation may have contributed. Further regression analysis leaving out the next two positive outliers of +423 and +355, who both had less than maximum CAPE scores, gave the same best subset of predictor variables with reduced CAPE score contributing significantly ($P < 0.0001$ (95% CI = −68 to −21)). The same best subset and significance of change in CAPE was observed also when the negative outlier of −634 was removed. Factors making no additional statistically significant contribution were age ($P = 0.25$), diagnosis of cancer ($P = 0.91$), number of previous operations in past 5 years ($P = 0.99$), pyrexia after operation ($P = 0.51$), duration of anaesthesia ($P = 0.91$), minimum mean arterial pressure ($P = 0.98$), self-rated quality of previous night's sleep ($P = 0.18$), and whether or not patients received bladder irrigation ($P = 0.48$). In addition, a separate regression analysis on patients who had $P\text{CO}_2$ values measured showed that minimum ($P = 0.80$) and maximum ($P = 0.10$) recorded $P\text{CO}_2$ values also made no additional statistically significant contribution. Figure 1 indicates patients with a known psychiatric disorder or history of stroke, and those having anaesthetic incidents. There were few of these patients, but inspection of the data for these individuals suggested that depressive illness, cerebrovascular disease and perioperative extremes of hypotension and hypercapnia may also contribute to impaired reaction time after operation.

DISCUSSION

Variability in reaction time performance was increased the day after anaesthesia in patients undergoing transurethral surgery. There was also evidence suggesting that learning of the task was impaired for up to 2 days after anaesthesia. The data are consistent with an earlier reaction time study in middle-aged patients, which used a similar control group of orthopaedic patients, and halothane anaesthesia, and in which performance was impaired for up to 48 h after anaesthesia [10]. However, only means of blocks of reaction time trials were reported, and it was not possible to compare our data directly. More recent studies reporting reaction time performances after alcohol or other drugs [15] in individuals indicate that an increase in the number of long responses also occurred, and that the mean measure was therefore a second order measure of drug effect [15].

The power of the study to examine the duration of changes in performance was reduced because the majority of transurethral patients were tested only at 24 h after operation. Similarly, assessment of the size of the performance deficit at 24 h in the transurethral group was compromised by having only a small control group of hospital patients. Also, there was marked improvement as a result of practice in some elderly patients. However, it is concluded that the 24-h performance deficit was related to the fact that transurethral patients had undergone surgery the day before, as there was no evidence in hospital or ambulant controls for increased variability in reaction time on the second occasion of testing. Further, transurethral surgical patients, in common with hospital controls, showed no difference in variability of reaction time 3 and 4 days after baseline testing. Even with transurethral procedures, it is difficult to establish that anaesthesia *per se* caused performance deficit, because of various confounding factors. However, we did take account of extent of surgery when analysing results.

Studies in young normal volunteers undergoing longer periods of anaesthesia but without surgery demonstrate that performance may be impaired for up to 1 week, depending on the solubility and metabolism of the general anaesthetic used [16].

Halothane would be expected to produce more mental impairment than enflurane, and this was suggested in the present study, but the evidence was weak. Chronological age was not a predictor of impaired performance and this is consistent with previous findings [7, 8]. In another study [6] which did show a positive correlation between age and performance deficit measured by tests of orientation and concentration, there was no control group, and a lack of standardization in anaesthetic and surgical procedures. Preoperative CAPE score correlated negatively with performance deficit 24 h after anaesthesia and this was statistically highly significant. The subscale of the CAPE we used is a short, screening version which can distinguish between groups of patients with different degrees of mental impairment [12], but is most successful if mental impairment is extreme, which was not the case in our patient sample. It is acknowledged that there is no validated screening test to measure mild mental impairment, but it is considered that questions of information and orientation are diagnostic [17]. It therefore appears reasonable to suggest that, as a group, patients scoring less than maximally on the CAPE are less capable mentally than a group who score maximally. Similarly, at this mild level of impairment it is not possible to determine cause. Forty-six percent of patients with reduced CAPE scores had evidence of cardiovascular disease, which was not significantly different from the incidence in maximally scoring patients (34%) and comparable to the proportion (37%) in general surgical patients older than 65 yr [18].

From surveys in the general population and diagnoses in hospital series of demented patients, it has been estimated that the prevalence of dementia may be as high as 10% in people aged more than 65 yr, with Alzheimer's disease accounting for up to 50% of cases and multi-infarct dementia for about 30% [19]. However, our study and others suggest that demented patients are less likely to be referred for surgery [18]. Our series included only one overtly demented patient with a CAPE score of 7, and apraxia, who was excluded. The association of reduced CAPE score and postoperative mental impairment is consistent with clinical observations after surgery indicating failing mental status as a predisposing factor [20]. Also, it has been reported that two patients described as having "organic brain disease" demonstrated a markedly impaired ability on a battery of performance tests following spinal with light general anaesthesia for prostatectomy [21]. The results of the present study indicate the importance of measuring variables which may confound performance, such as sedative drugs and postoperative pain. Similarly, the results emphasize the importance of measuring all clinical details. Whilst hypotension and changes in $P\text{CO}_2$ were not associated with performance deficit in the whole series, there was evidence, as shown in earlier work [22, 23], that extremes of hypotension and hypercapnia may be associated with performance deficit. It was of interest that the patient with depression also showed a large performance deficit. It has been suggested in other studies that depression, antidepressant drugs, or both may predispose to impaired performance after anaesthesia and this merits further study [5].

In conclusion this study has indicated that chronological age does not contribute to any postoperative performance deficit, but that preoperative mental impairment has a large influence. It has also indicated other risk factors worthy of examination in follow-up studies of patients undergoing longer and more complicated anaesthesia alongside more extensive surgery, where the complex clinical situation makes investigation more difficult, but where the anaesthetic risks are greater. Such studies should include more detailed screening of preoperative mental impairment.

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COMPARISON OF SUFENTANIL–NITROUS OXIDE ANAESTHESIA WITH FENTANYL–NITROUS OXIDE ANAESTHESIA IN GERIATRIC PATIENTS UNDERGOING MAJOR ABDOMINAL SURGERY†

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SUMMARY

We have measured haemodynamic changes and plasma concentrations of catecholamines during sufentanil–nitrous oxide and fentanyl–nitrous oxide anaesthesia in a controlled, randomized, double-blind study of 20 geriatric patients (age 65–86 yr) undergoing major abdominal surgery. Fentanyl 7 $\mu g\ kg^{-1}$ followed by infusion of 3 $\mu g\ kg^{-1}\ h^{-1}$ was compared with sufentanil 1 $\mu g\ kg^{-1}$ followed by 0.4 $\mu g\ kg^{-1}\ h^{-1}$. The opioid was supplemented with 60–67% nitrous oxide in oxygen. Haemodynamic changes, plasma concentrations of catecholamines (by high pressure liquid chromatography) and opioids (by radioimmunoassay), and myocardial lactate extraction were measured in the awake state, and at defined times during anaesthesia and surgery. Haemodynamic state was stable during induction and tracheal intubation in both groups, while during stressful operative periods there were increases in mean arterial pressure (17% in the fentanyl group; 11% in the sufentanil group), heart rate (fentanyl 20%, sufentanil 14%) and plasma concentrations of catecholamines (adrenaline: fentanyl 316%, sufentanil 86%; noradrenaline: fentanyl 78%, sufentanil 186%) in both groups. Sufentanil was similar to fentanyl in attenuating the haemodynamic and hormonal responses to surgical stimulation. In two patients in the fentanyl group and three in the sufentanil group, myocardial lactate production was observed temporarily, indicating myocardial ischaemia caused by surgical stress.

KEY WORDS

Anaesthesia geriatric. Analgesics: fentanyl, sufentanil Surgery: haemodynamic responses, hormonal responses.

Anaesthesia in geriatric patients requires minimal depression of cardiac and circulatory functions, as cardiovascular reserve is diminished in old age [1]. Often, a balanced technique using fentanyl is used in these patients, as fentanyl has a rapid onset of action [2], good cardiovascular stability [2–4] and does not release histamine [5]. However, fentanyl–nitrous oxide–neuromuscular blocker anaesthesia may not block sympathoadrenal responses to surgical stimulation and may result in prolonged respiratory depression during the postoperative period.

Anaesthesia with sufentanil (the 5–10 times more potent N-4-thienyl derivative of fentanyl) has been reported to produce better suppression of stress responses than fentanyl [6–9], and greater postoperative analgesia with less respiratory depression [10]; in other studies no difference was noted [3, 11–15]. However, most of the previous studies have been performed in patients undergoing coronary artery bypass grafting using high doses of the opioid.

This study was designed to compare the effects of the two opioids in geriatric patients using standard doses.

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PATIENTS AND METHODS

Patients

After approval by the Göttingen University Human Subjects Review Committee and written informed consent, we studied 20 ASA II or III patients (aged at least 65 yr) undergoing major abdominal surgery in a controlled, randomized, double-blind study. Surgery comprised: gastrectomy, partial pancreatectomy, partial resection of intestine or exploratory laparotomy (inoperable cases). The types of operation and blood loss were similar in both groups (table I). Patients with coronary heart disease were included in the study; those with angina at rest, heart failure, valvular heart disease or arrythmias were excluded. There were no significant differences between groups in age, body weight or pre-existing disease states (table I). The patients were allocated to one of the two groups at random, but there was by chance a different sex ratio between the groups. All patients were premedicated with lormetazepam 2 mg by mouth the night before the operation and also 1 h before arrival in the anaesthetic room. All patients received 750–1000 ml of a balanced electrolyte solution during insertion of catheters and the resting period.

TABLE I. *Patient characteristics and duration of anaesthesia*

	Sufentanil group ($n = 10$)	Fentanyl group ($n = 10$)
Sex (M/F)	8/2	5/5
Age (yr)		
Mean	75	75
Range	67–81	65–86
Weight (kg)		
Mean	74	69
Range	50–84	60–86
Hypertension	5	5
Angina	3	3
Coronary heart disease	5	4
Myocardial infarction > 6 months earlier	3	1
Diabetes mellitus	2	1
Chronic obstructive lung disease	2	1
Duration of operation (h)		
Mean (SD)	3.3 (2.3)	2.8 (1.3)
Range	1.0–6.5	1.7–6 0
Upper abdominal surgery	6	4
Lower abdominal surgery	4	6
Blood loss (ml)		
Mean (SD)	830 (620)	880 (570)

Monitors and measurements

A three-lead electrocardiograph (Hellige) and a Lifescan brain activity monitor (Braun) were attached in the induction room, and the following catheters were inserted percutaneously under local anaesthesia: a Goodale–Lubin catheter (7-French gauge, USCI) into the coronary sinus via the right internal jugular vein for blood sampling; a flow-directed pulmonary artery catheter (Vygon quadruple thermodilution Thermocath) via the left internal jugular vein for measurement of pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure and cardiac output (the position of the catheters was confirmed by fluoroscopy); a 20-gauge indwelling cannula into the non-dominant radial artery for continuous monitoring of arterial pressure and blood sampling; and two 14-gauge indwelling cannulae into peripheral veins for administration of drugs and fluids.

The processed EEG and its median frequency were displayed continuously on the Lifescan monitor. The ECG, systemic arterial, pulmonary arterial and central venous pressures were displayed continuously on the patient monitor and recorded simultaneously on a 10-channel chart recorder (Hellige). Cardiac output was measured by the thermodilution technique using 10 ml of saline solution at 0 °C (cardiac output computer, Fisher BN 7206); the mean of three consecutive values was taken. Measurements of cardiac output and wedge pressure were performed at the end of expiration. After each measurement of cardiovascular variables, blood samples were obtained simultaneously from the coronary sinus and the radial artery and analysed for $P\text{O}_2$, $P\text{CO}_2$, pH, base excess and standard bicarbonate (IL 282, Instrumentation Laboratories), electrolyte concentrations by flame photometry (IL 543, Instrum. Lab.), and lactate (standard test combination, Boehringer). Arterial samples were obtained for measurement of plasma concentrations of catecholamines (by high pressure liquid chromatography with fluorescence detection [16]) and fentanyl or sufentanil (by radioimmunoassay, Janssen).

Procedure

Baseline measurements were made after 30 min of rest; after preoxygenation, pancuronium 1 mg was given i.v. as a bolus dose for precurarization. In the fentanyl group, anaesthesia was induced with fentanyl 7 μg kg^{-1} followed by a continuous infusion of 3 μg kg^{-1} h^{-1} for maintenance. In the sufentanil group, patients received 1 μg kg^{-1} as a bolus and 0.4 μg kg^{-1} h^{-1} for maintenance. As the anaesthetic potency of sufentanil was considered to be approximately 7 times that of fentanyl, this dose regimen was assumed to be equipotent [11]. The drugs were diluted such that the volumes administered were equal in both groups, and the syringes were labelled as "opioid" to preserve the double-blind nature of the study.

After injection of the opioid, assisted ventilation via a face mask was used to maintain Pa_{CO_2} at 5.0–5.3 kPa as confirmed by arterial blood-gas analyses and continuous measurement of the end-expiratory carbon dioxide concentration (Multicap monitor, Datex). Five minutes after injection of the opioid and after completion of the second measurements, etomidate 0.2 mg kg^{-1} and suxamethonium 1 mg kg^{-1} were given in both groups. The trachea was intubated and anaesthesia was maintained with 60–67% of nitrous oxide in oxygen to the end of operation and with the opioid infusion to approximately 30 min before the end of operation.

The infusion rate was increased and additional boluses of fentanyl 0.15 mg or sufentanil 21 μg were administered when signs of insufficient depth of anaesthesia developed—notably: increase in systolic arterial pressure by more than 15%; tachycardia if not caused by deficiency of volume or blood loss; tears; sweating; movement; increase in EEG median frequency up to the individual baseline value. All patients were given pancuronium. This anaesthetic technique resulted in an average consumption of fentanyl 390 μg h^{-1} or sufentanil 59 μg h^{-1} during a mean time of anaesthesia of 3.9 (SD 1.3) h (fentanyl) or 4.3 (2.1) h (sufentanil).

Measurements were performed at the following times: I = baseline values in the awake patients after insertion of the catheters and a resting period of 30 min; II = 5 min after injection of the opioid bolus; III = 2 min after tracheal intubation; IV = 5 min before the beginning of surgery; V = 2 min after skin incision; VI = 2 min after opening of the peritoneum; VII = 2 min after the end of the operation (defined as the end of the skin suture) and termination of the administration of nitrous oxide.

Data analysis

Cardiac index was calculated by dividing cardiac output by the body surface area. The myocardial lactate extraction was calculated by dividing the arterial–coronary sinus blood lactate concentration difference by the arterial lactate concentration and multiplying by 100.

All data are given as mean (SD). The Mann–Whitney U test was used to compare data of all patients between groups. The Wilcoxon test was used for statistical analysis of the data within each group at different times of measurement. $P < 0.05$ was taken as significant.

RESULTS

Both groups were similar in age, body weight and number of patients with hypertension or coronary heart disease (table I). No patient suffered from angina during the preoperative period or the period of observation. Arterial pressure was increased in three patients in the fentanyl and two in the sufentanil group on arrival in the anaesthetic room and remained increased even after a resting period of 30 min. These patients were known to be hypertensive. Baseline cardiac index was increased in 50% of the patients (fig. 1). This is not surprising, as the normal value for cardiac index of approximately 3.0 litre min^{-1} m^{-2} may increase by nearly 50% with anxiety [17]. (Nearly all patients were undergoing surgery for malignancy.)

One patient in the fentanyl group and three in the sufentanil group developed chest wall rigidity after administration of the opioid.

There were no significant differences between the groups during the study. Haemodynamic variables remained stable with both drugs after induction, tracheal intubation and the beginning of the operation (figs 1–3; table II). Severe surgical stimulation (measurement VI) resulted in increases in arterial pressure (mean values for fentanyl and sufentanil, respectively, 17% and 11%) (fig. 2), heart rate (fentanyl 20%, sufentanil 14%) (fig. 3), and plasma concentrations of adrenaline (fentanyl 316%, sufentanil 86%) (table III, fig. 4) and noradrenaline (fentanyl 78%, sufentanil 186%) (fig. 5), compared with baseline values. In two patients in each group, additional boluses of the opioid failed to attenuate these reactions and halothane or nitroglycerin was given to these patients for approximately 32 min (mean) after measurement VI.

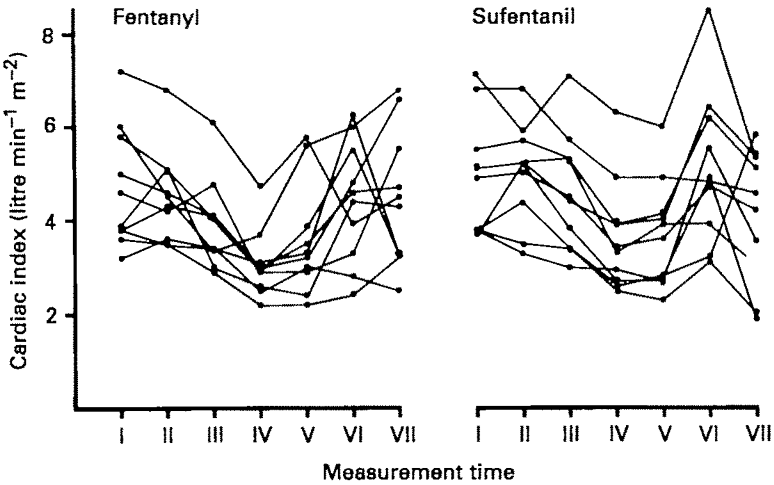

FIG. 1. Cardiac index. I = Awake; II = 5 min after induction; III = 2 min after intubation; IV = 5 min before skin incision; V = 2 min after incision; VI = 2 min after opening of the peritoneum and insertion of hooks; VII = 2 min after the end of the operation. No significant difference between groups.

TABLE II. *Haemodynamic variables (mean (SD)) after sufentanil (S) (n = 10) or fentanyl (F) (n = 10). I = Awake; II = 5 min after injection of opioid; III = 2 min after intubation; IV = 5 min before the operation; V = 2 min after skin incision; VI = 2 min after opening of the peritoneum and insertion of hooks; VII = end of operation.* $P < 0.05$: **compared with I*

	Group	I	II	III	IV	V	VI	VII
Heart rate	S	77 (12)	79 (13)	74 (12)	68 (12)*	68 (13)*	88 (19)	93 (23)
(beat min^{-1})	F	74 (10)	73 (12)	69 (16)	60 (8)*	69 (13)	89 (15)	89 (20)
Systolic arterial	S	168 (19)	156 (35)	158 (34)	132 (40)*	146 (30)	176 (48)	164 (37)
pressure (mm Hg)	F	165 (30)	159 (33)	167 (45)	138 (27)*	152 (29)	179 (46)	173 (27)
Diastolic arterial pressure	S	79 (6)	71 (8)	68 (8)	66 (15)	76 (16)	82 (24)	84 (14)
(mm Hg)	F	73 (12)	72 (12)	76 (18)	71 (12)	77 (16)	87 (25)	81 (20)
Mean arterial pressure	S	109 (11)	104 (17)	97 (12)	94 (19)*	99 (17)	121 (28)	111 (18)
(mm Hg)	F	109 (18)	108 (17)	105 (26)	94 (13)*	107 (16)	127 (20)*	119 (20)
Mean pulmonary arterial	S	21 (5)	24 (9)	24 (6)	23 (10)	25 (9)	30 (13)*	24 (8)
pressure (mm Hg)	F	21 (3)	24 (6)	25 (7)	19 (3)	22 (3)	28 (5)*	20 (4)
Mean pulmonary capillary	S	12 (4)	13 (6)	12 (6)	12 (3)	14 (4)	17 (6)*	12 (4)
wedge pressure (mm Hg)	F	11 (3)	14 (3)	12 (3)	12 (2)	16 (2)	20 (4)*	12 (5)
Central venous pressure	S	5.6 (2.8)	7.8 (3.6)	6.6 (2.4)	8.0 (1.9)*	10.9 (3.4)*	11.0 (2.9)*	8.8 (3.7)*
(mm Hg)	F	5.9 (3.2)	9.1 (3.9)*	9.2 (3.5)*	8.6 (2.0)*	10.6 (2.3)*	13.6 (3.4)*	8.6 (2.9)
Cardiac index	S	5.0 (1.2)	5.0 (1.1)	4.6 (1.3)	3.7 (1.2)*	3.7 (1.1)*	5.2 (1.6)	4.1 (1.4)
(litre min^{-1} m^{-2})	F	4.7 (1.3)	4.5 (1.0)	3.9 (1.0)	3.0 (0.7)*	3.6 (1.2)*	4.4 (1.3)	4.5 (1.4)

There was no correlation between arterial pressure, heart rate, catecholamine concentrations and EEG. Patients with known hypertension had greater mean baseline values of arterial pressure (fentanyl 117 mm Hg; sufentanil 116 mm Hg) than the other patients (102 mm Hg and 101 mm Hg, respectively). At measurement IV, when the relative depth of anaesthesia was maximum, mean arterial pressure was not significantly different for hypertensive patients (fentanyl 98 mm Hg, sufentanil 93 mm Hg) compared with normotensive subjects (fentanyl 90 and sufentanil 95 mm Hg). Surgical stimulation (measurement VI), however, caused greater increases in mean arterial pressure in hypertensive patients (fentanyl 139 mm Hg, sufentanil 133 mm Hg) than in other patients (fentanyl 116 and sufentanil 108 mm Hg). Sufentanil was not superior to fentanyl in preventing increases in arterial pressure. At the end of the operation (measurement VII), heart rates and plasma concentrations of catecholamines were maximum. Nearly all patients (eight receiving fentanyl, seven receiving sufentanil) were awake, most of these breathing spontaneously (six re-

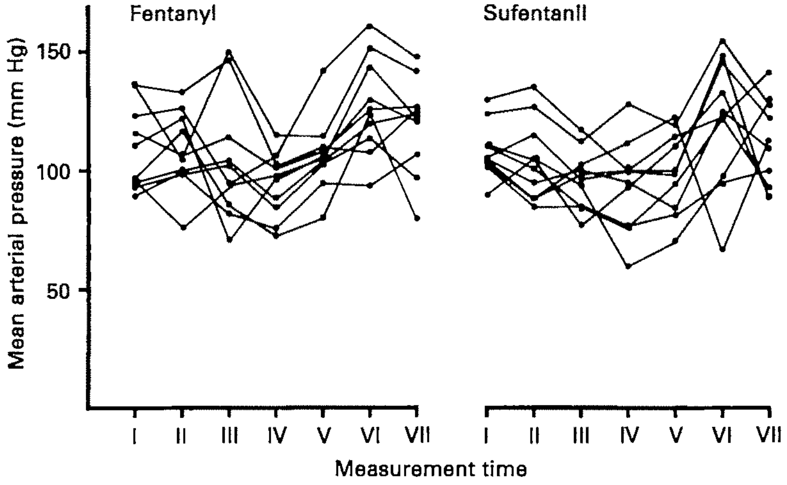

FIG. 2. Mean arterial pressure. (For explanation of measurement times, see legend to figure 1.) No significant difference between groups.

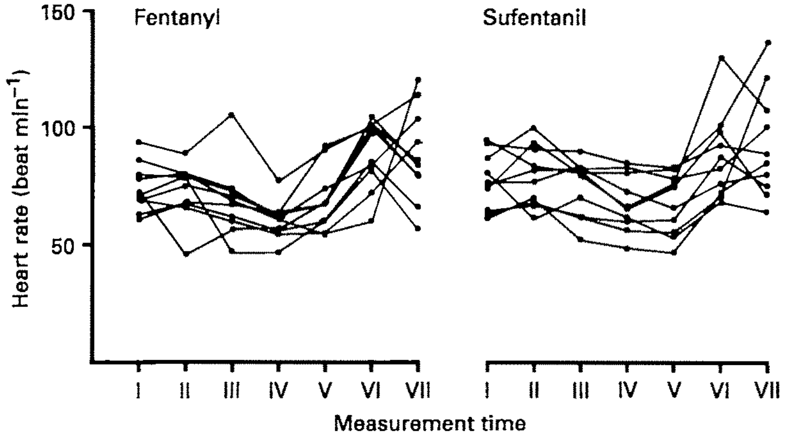

FIG. 3. Heart rate. (For explanation of measurement times, see legend to figure 1.) No significant difference between groups.

TABLE III *Arterial plasma concentrations of opioids and catecholamines, myocardial lactate extraction and EEG median frequency. Legend as defined in table II.* $P < 0.05$ *: *compared with I; †S compared with F*

	Group	I	II	III	IV	V	VI	VII
Opioid concn (ng ml^{-1})	S	0.0	1.3 (0.3)	0.9 (0.7)	0.5 (0.3)	0.5 (0.2)	0.8 (0.5)	0.3 (0.2)
	F	0.0	7.1 (3.5)	4.6 (1.8)	4.5 (2.1)	4.6 (2.5)	3.0 (1.3)	3.6 (1.2)
Adrenaline concn (pg ml^{-1})	S	154 (75)	99 (69)*†	56 (35)*	43 (29)*	120 (98)	284 (248)	1035 (1274)*
	F	99 (89)	243 (241)*†	70 (82)	42 (48)*	146 (141)	412 (546)	1147 (1315)*
Noradrenaline concn (pg ml^{-1})	S	190 (90)	258 (144)	231 (132)	228 (186)	247 (133)	543 (164)*	787 (417)*
	F	261 (253)	328 (231)	284 (161)	167 (89)	280 (140)	465 (195)*	805 (586)*
Myocardial lactate extraction (%)	S	20.1 (16.3)	23.2 (21.5)	27.9 (20.8)	22.3 (19.7)	19.3 (19.6)	11.2 (15.8)*	10.8 (12.8)*
	F	14.8 (14.2)	19.5 (10.5)	16.4 (16.0)	9.0 (10.9)	9.4 (10.6)	7.1 (7.8)*	10.7 (10.6)
EEG median	S	9.1 (3.2)	3.8 (3.2)*	5.2 (2.2)*	2.8 (1.9)*	3.8 (2.7)*	3.7 (2.1)*	8.1 (3.7)
	F	8.7 (3.4)	3.8 (2.7)*	5.3 (3.0)*	2.8 (2.7)*	3.5 (3.2)*	4.8 (2.9)*	8.8 (4.4)

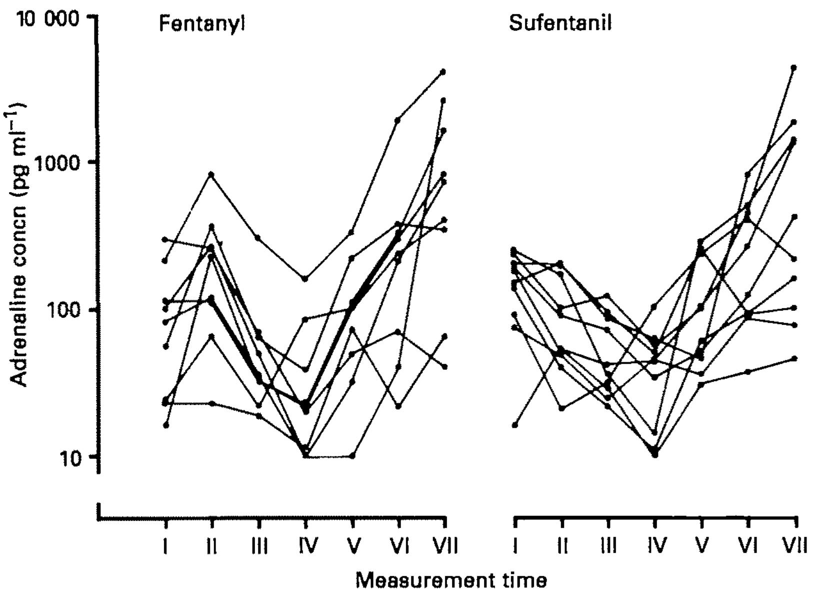

FIG. 4. Plasma concentrations of adrenaline. (For explanation of measurement times, see legend to figure 1.) No significant difference between groups.

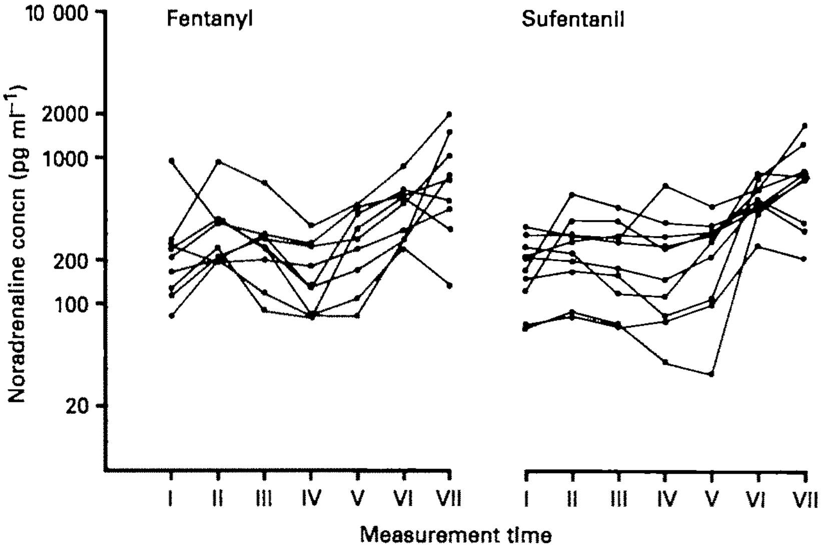

FIG. 5. Plasma concentrations of noradrenaline. (For explanation of measurement times, see legend to figure 1.) No significant difference between groups.

ceiving fentanyl, five receiving sufentanil). As the body temperature of most patients was low and the operations had been extensive in most, only three patients in the sufentanil group could undergo immediate tracheal extubation. The other patients were sedated and underwent artificial ventilation for periods of 2 h to 15 days after operation.

Two patients in the fentanyl group and three in the sufentanil group temporarily showed production of myocardial lactate during stressful operative periods (fig. 6). No electrocardiographic evidence of myocardial ischaemia was obvious in these or any of the other patients using ECG lead II, and no patient developed myocardial infarction during the postoperative period.

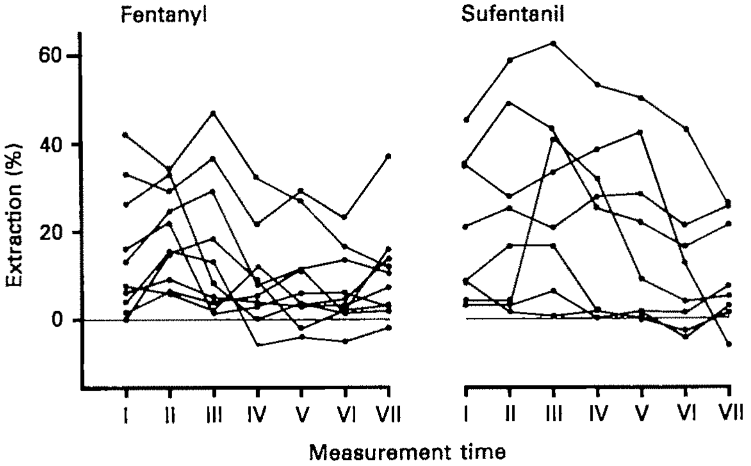

FIG. 6. Myocardial lactate extraction. (For explanation of measurement times, see legend to figure 1.) No significant difference between groups.

DISCUSSION

Fentanyl and sufentanil are suitable for anaesthesia in geriatric patients because of minimal cardiovascular effects [5, 12]. Many studies have been performed comparing sufentanil with fentanyl, mostly in patients undergoing high-dose opioid anaesthesia for cardiac surgery, but few studies have been undertaken in patients undergoing non-cardiac surgery and with smaller doses. Clark and colleagues [10] reported similar haemodynamics and plasma concentrations of catecholamines after sufentanil 2 μg kg^{-1} and fentanyl 15 μg kg^{-1}, but patients in the sufentanil group had better analgesia and less respiratory depression 30 min after operation.

The double-blind comparisons of these opioids [14, 15] showed no difference in haemodynamic state using seven-fold or 10-fold greater dosage of fentanyl compared with sufentanil. Flacke and colleagues [9] described the only double-blind comparison of sufentanil and fentanyl (and two other opioids) with apparently better results in the sufentanil group. They investigated 60 patients in four groups (corresponding to the four opioids), each group consisting of dissimilar operations, and the patients were not assigned equally to the types of operations. Cardiovascular stability was better in the sufentanil group, probably because of less surgical stress compared with the other groups.

In our study, only patients undergoing major abdominal surgery were included. However, the duration of surgery was different between groups (table I). However, all patients were investigated under standardized, similar conditions from measurements I to VI. Only at measurement VII may the different duration of surgery have possibly influenced the results.

Our dosage regimen resulted in a mean consumption of fentanyl 390 μg h^{-1} and of sufentanil 59 μg h^{-1}—a ratio of 6.6:1. The same potency ratio was found by Thomson and colleagues [11], who described sufentanil 15 μg kg^{-1} as clinically indistinguishable from fentanyl 100 μg kg^{-1} when used as the primary anaesthetic agent for coronary artery surgery.

All cardiovascular variables were stable in both groups after induction of anaesthesia. No patient in the sufentanil group and only two in the fentanyl group exhibited changes in heart rate or arterial pressure after intubation. Five minutes before skin incision, when the relative depth of anaesthesia was maximum in both groups, some patients developed bradycardia and a marked decrease in the mean arterial pressure, but not to critical values.

There was no interindividual correlation between depth of anaesthesia and plasma concentrations of opioids, probably because the latter do not represent concentrations at the opioid receptor sites. The correlation between EEG median frequency and depth of anaesthesia was poor in most patients. These findings are in accordance with those of Bovill, Sebel and Stanley, who reported that the relationship between opioid analgesic dose, central nervous system opioid receptor occupancy and ablation of consciousness and awareness was obscure [4].

As coronary heart disease is common in old age and previous myocardial infarction is associated with increased frequency of postoperative myocardial infarction [18], perioperative myocardial infarction is a major complication of anaesthesia in geriatric patients. Two patients in the fentanyl group and three in the sufentanil group exhibited anaerobic myocardial metabolism leading to lactate release into the coronary sinus blood, probably as a result of transient myocardial ischaemia, although there were no electrocardiographic changes. Roy, Edelist and Gilbert observed ECG ischaemia in 38% of 29 patients with known coronary artery disease during non-cardiac surgery, with one case of postoperative myocardial infarction [19]. They reported that lead V_5 analysis was superior to lead II analysis in detecting ST segment depression. De Bruijn [20] recognized 96% of all intraoperative episodes with leads II, V_4, and V_5, compared with only 33% with lead II alone. As we used only ECG lead II and no precordial ECG, it is possible that temporary ST segment depression was not evident in our investigation. However, no patient in our study developed myocardial infarction after operation.

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EFFECTS OF FLUMAZENIL ON CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION AFTER MIDAZOLAM ANAESTHESIA FOR CRANIOTOMY

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SUMMARY

Cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR_{O_2}) were measured by a modification of the Kety–Schmidt technique using i.v. xenon-133 in 20 patients undergoing craniotomy for supratentorial cerebral tumours. Anaesthesia was induced and maintained with midazolam, fentanyl and nitrous oxide. Pancuronium was given for neuromuscular block. The lungs were ventilated to normocapnia. The first flow measurements were performed approximately 1 h after induction of anaesthesia. At the end of operation the patients were allocated to two groups. Ten patients were given flumazenil 0.01 mg kg^{-1} and 5 min later the second flow measurement was performed. In the other 10 patients the second flow measurement was performed before the administration of flumazenil. Plasma concentrations of midazolam were measured at the time of each measurement of CBF. There was no difference between the groups in plasma concentration of midazolam, CBF or CMR_{O_2}. Flumazenil had no effect on CBF and CMR_{O_2}.

KEY WORDS

Anaesthesia · neurosurgical Anaesthetics, intravenous: midazolam Antagonists, benzodiazepine: flumazenil. Brain: cerebral blood flow, CMR_{O_2}

Flumazenil is an imidazobenzodiazepine which inhibits the central effects of the benzodiazepine by competitive interaction at specific receptors [1]. The cerebrovascular effects of flumazenil may be clinically relevant as flumazenil may be useful to antagonize benzodiazepines at the end of neurosurgical operations.

The purpose of the present study was to determine if flumazenil had any effect on cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR_{O_2}) when administered after midazolam.

PATIENTS AND METHODS

Patients

Patients with supratentorial cerebral tumours and midline shift < 10 mm estimated by CT scanning gave informed consent to the study, which was approved by the local Ethics Committee. Patients were excluded if they had evidence of heart disease, hypertension or chronic pulmonary disease. Before operation, all patients were awake, orientated and without major neurological deficit. All patients were being treated with dexamethasone 6 mg four times daily.

The patients were premedicated with diazepam 10–20 mg orally 2 h before operation. After preoxygenation, anaesthesia was induced with midazolam 0.3 mg kg^{-1} and fentanyl 4 µg kg^{-1}. Pancuronium 0.15 mg kg^{-1} was given and the lungs ventilated manually until paralysis was complete. Approximately 1 min before tracheal intubation, lignocaine 1.5 mg kg^{-1} was given i.v.

After tracheal intubation, anaesthesia was maintained with midazolam 0.65 mg kg^{-1} h^{-1} for 15 min, followed by 0.125 mg kg^{-1} h^{-1}. This infusion regimen was expected to result in a steady-state concentration of about 300 ng ml^{-1} from 45 min onwards [2]. The first CBF measurement

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TABLE I. *Midazolam*, Pa_{CO_2}, *rectal temperature, CBF*, $(Ca_{O_2}-Cv_{O_2})$ *and* $CMRo_2$ *in patients undergoing craniotomy for supratentorial cerebral tumours (median (range))*

	Midazolam (ng ml^{-1})	Pa_{CO_2} (kPa)	MAP (mm Hg)	Temp. (°C)	CBF (ml min^{-1}/100 g)	$(Ca_{O_2}-Cv_{O_2})$ (vol %)	$CMRo_2$ (ml min^{-1}/100 g)
Group 1							
CBF1	375	4.05	78	35.7	23	8.9	2.1
	(240–500)	(3.6–4.8)	(65–110)	(35–37)	(16–42)	(3.8–14.2)	(1.1–3.2)
CBF2	490	3.95	93	35.6	21	7.8	1.6
	(420–600)	(3.2–4.3)	(70–105)	(35–37)	(17–46)	(4.9–12.6)	(1.2–3.6)
Group 2							
CBF1	280	4.50	76	36.2	24	9.4	2.3
	(190–452)	(3.5–5.1)	(64–112)	(35–37)	(21–36)	(5.3–13.3)	(1.6–3.0)
CBF2	418	4.05	82	36.4	22	8.1	2.1
	(360–600)	(3.3–5.0)	(61–90)	(35–37)	(14–38)	(2.2–14.1)	(1.7–3.0)

was performed at a median time of 80 min (range 52–135 min) after induction, and before incision. Subsequently, the patients were given a bolus of midazolam 0.3 mg kg^{-1} and the infusion rate increased to 0.25 mg kg^{-1} h^{-1}. The lungs were ventilated with 66 % nitrous oxide in oxygen, followed by adminstration of fentanyl 4 µg kg^{-1} h^{-1} and pancuronium 1–2 mg—sufficient to provide neuromuscular block estimated by train-of-four stimulation. Ventilation was controlled to achieve a Pco_2 of 4 kPa, as determined by arterial blood-gas analysis (ABL-3, Radiometer, Copenhagen, Denmark). Rectal temperature was measured repeatedly and mean arterial pressure (MAP) measured continuously via a radial artery cannula which was used also for blood sampling.

After the first CBF measurement, mannitol 0.5 g kg^{-1} was administered i.v. over 5 min.

The patients were allocated randomly to two groups: in group 1 ($n = 10$), at the end of the craniotomy, flumazenil 0.01 mg kg^{-1} was administered and 5 min later the CBF measurement was repeated; in group 2 ($n = 10$), at the end of the craniotomy the CBF measurement was performed and flumazenil 0.01 mg kg^{-1} administered.

Measurement of CBF and $CMRo_2$

After induction of anaesthesia, a catheter was introduced percutaneously into the internal jugular vein with the tip of the catheter at the base of the skull. Xenon-133 (3 mCi dissolved in saline 30 ml) was injected i.v. over a period of 20 min. During a 30-min desaturation period, 2-ml blood samples were withdrawn from the arterial and the internal jugular vein catheters at exact time intervals. Radioactivity was counted in a well counter (Berthold LB MAG 510). CBF was calculated according to the i.v. modification [3] of the height-over-area formula of the classical Kety–Schmidt method [4].

The arterio–venous oxygen difference $(Ca_{O_2}-Cv_{O_2})$ was calculated as the difference in oxygen content between arterial and jugular venous blood calculated from the oxygen saturation, Po_2 and haemoglobin concentration of the samples. $(Ca_{O_2}-Cv_{O_2})$ was measured in duplicate at each CBF measurement. $CMRo_2$ was calculated as the product of $(Ca_{O_2}-Cv_{O_2})$ and CBF.

Simultaneously with each CBF measurement (5 min before and after desaturation of xenon-133), 5-ml arterial blood samples were withdrawn, and the plasma stored at −20 °C for analysis of midazolam concentration by gas chromatography (Roche, Basle).

Statistical analysis

Data were analysed by Wilcoxon test for paired data and Mann–Whitney test for unpaired data. $P < 0.05$ was considered significant.

RESULTS

The median age of the patients (14 male, six female) was 48 yr (range 21–71 yr). There were no significant differences between the groups in sex, age, weight, histologic diagnosis of tumour or tumour size. The first CBF measurement was performed at a median time of 80 min (range 52–135 min) after induction, and before incision; the second was performed at the end of the craniotomy at a mean 185 min (range 120–270 min) after the first flow measurement.

There were no differences between the groups in plasma concentration of midazolam or Pa_{CO_2}. MAP was constant during flow measurements. At the first flow measurement, there was no difference, but at the second measurement MAP increased in the group which received flumazenil. There were no differences in $CMRo_2$ or CBF within or between the groups (table I).

DISCUSSION

We have shown that flumazenil did not have any effect on CBF or $CMRo_2$ when administered after midazolam anaesthesia in neurosurgical patients.

In an animal study [5], flumazenil was found to have no effect on cerebral metabolic rate, but there was a decrease in MAP, and an increase in CBF and intracranial pressure (ICP). In another study [6], flumazenil was evaluated in 18 patients following craniotomy for tumour or aneurysm surgery. Flumazenil induced rapid recovery after prolonged administration of midazolam, enabling the surgeon to perform an accurate neurological assessment. In patients with severe head injury and unstable ICP sedated with midazolam, an increase in ICP has been reported after administration of flumazenil [7]. A study in human volunteers demonstrated absence of effects of flumazenil on CBF when injected alone, and the efficacy of flumazenil in antagonizing the depressant effects of midazolam on cerebral haemodynamics [8].

CBF and $CMRo_2$ were measured peroperatively during craniotomy for supratentorial cerebral tumours. Regional flow differences have been observed in patients with cerebral tumours, close to the tumour region [9] and in regions remote from the tumour [10].

In the present study, flow measurements were performed in patients with small cerebral tumours without greater midline shift; thus the CBF and $CMRo_2$ values obtained may be affected mostly by the large preponderance of normal brain tissue.

Cerebral blood flow was measured using an i.v. modification of the inhalation method described by Kety and Schmidt [4]. This technique has been validated for CBF measurements in awake patients with supratentorial cerebral tumours [3]. The values found corresponded with values found in normal man, which argues against a major influence of tumour on global CBF. Furthermore, this technique has produced reliable results in repeated CBF studies [11].

As mannitol causes an increase in CBF 10–20 min after a bolus dose [12], and a variable increase in $CMRo_2$ [12, 13], it was decided to treat all patients in this study with mannitol. Thus the influence of mannitol on cerebral circulation and metabolism should be comparable in both groups.

The midazolam–fentanyl anaesthesia was tolerated well in all patients, and provided good surgical conditions. Flumazenil provoked rapid and complete recovery after midazolam anaesthesia. None of the patients required artificial ventilation after operation and they were all awake and co-operative. A few of the patients required further doses of flumazenil because the degree of sedation increased after a period of 30–120 min.

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PAIN ON INJECTION OF PROPOFOL: EFFECTS OF CONCENTRATION AND DILUENT

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SUMMARY

The emulsion formulation of propofol (Diprivan) evokes pain on i.v. injection, although its pH and osmolality are close to those of blood. The pain induced by serial dilutions of propofol in Intralipid and 5% glucose was examined in isolated vein segments and after intracutaneous injection. Propofol evoked pain in a concentration-related manner in six of eight subjects after i.v. perfusion and in all eight subjects after intracutaneous injections. Pain was maximal with propofol 56×10^{-3} mol litre^{-1} when visual analogue pain scale was 60% of maximum (range 20–92%) for venous perfusion and 89% (range 66–100%) for intracutaneous injection. Dilution with 10% Intralipid reduced pain more than that with 5% glucose. We conclude that the intensity of pain after i.v. injection of propofol was related to its free aqueous concentration.

KEY WORDS

Anaesthetics, intravenous. propofol. Complications: pain on injection.

Many anaesthetic induction agents, sedatives and neuromuscular blocking drugs are formulated at a non-physiological osmolality or pH (> 3 osmol kg^{-1}, pH < 4 or > 11), which may be associated with pain on injection [1]. However, propofol evokes pain in 10–100% of patients [2–5], although the solution (Diprivan, ICI) has almost normal osmolality and pH (0.303 osmol kg^{-1}; pH 8.0). This suggests that the substance itself is responsible for the pain evoked. To test this hypothesis, we have examined the relationship between pain intensity and concentration by perfusing serial dilutions of propofol through a vascularly isolated segment of a dorsal hand vein and by intracutaneous injections into the forearm.

Because the free concentration in the aqueous phase of highly lipophilic agents such as propofol depends on the proportion of lipid in the emulsion, we studied the effects of propofol as dilutions of Diprivan with 5% glucose and with 10% Intralipid.

SUBJECTS AND METHODS

Eight healthy subjects (physicians and medical students) volunteered and consented to the study, which was approved by the Committee on Medical Ethics of the University of Düsseldorf. Experiments started at 09:00 with the subjects sitting comfortably semirecumbent at a thermoneutral room temperature of 24 °C. A vein segment devoid of side branches between two valves was identified on the dorsum of the non-dominant hand. Two 14-gauge Teflon cannulae (Venflon, Viggo) were inserted from down- and upstream puncture sites. The vein segment was isolated from the systemic circulation by external air pad occluders in order to avoid systemic effects of propofol and expose the vein wall to known drug concentrations.

The completeness of the isolation of the vein segment was ascertained by absence of visible blood in the effluent and by the similarity between inflow (delivered by a calibrated precision pump) and outflow (sampled continuously in a calibrated cylinder and measured every 1 min). Two experiments were terminated because of discrepancies

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TABLE I. *Time course (s) (median (range)) of pain after intracutaneous injections and i.v. perfusions of propofol at varying concentrations with 5% glucose or Intralipid as diluent*

	I.v. perfusions ($n = 6$)				Intracutaneous injections ($n = 8$)			
	Intralipid		5% Glucose		Intralipid		5% Glucose	
Propofol concn (mol litre^{-1})	Latency	Time to recovery	Latency	Time to recovery	Latency	Duration	Latency	Duration
0.0×10^{-3}	—	—	—	—	—	—	—	—
3.5×10^{-3}	—	—	188 (86–305)	64 (45–90)	—	—	25 (6–36)	18 (11–25)
7.0×10^{-3}	—	—	79 (12–182)	82 (31–126)	23 (7–35)	30 (16–48)	17 (8–23)	44 (11–67)
14.0×10^{-3}	319 (205–455)	20 (18–22)	61 (27–192)	133 (47–255)	24 (8–31)	65 (15–117)	11 (4–19)	61 (14–135)
28.0×10^{-3}	165 (25–335)	61 (15–146)	31 (9–71)	170 (88–233)	9 (5–17)	81 (21–145)	8 (3–15)	97 (22–171)
56.0×10^{-3}	24 (11–55)	159 (42–267)	17 (9–46)	151 (61–283)	6 (3–9)	127 (27–198)	6 (2–8)	135 (35–220)

between in- and outflowing volumes; these were followed by transitory systemic effects of propofol (slight vertigo and impaired visual acuity).

The subjects rated their pain intensity on a visual analogue scale with the help of apparatus of our own design. A handle could be moved over a distance of 80 mm to the right. A linear pontentiometer gave a voltage proportional to the rated pain intensity between 0 (no pain) and 100% (maximum tolerable pain) which was recorded continuously on a Gould TA 500 Polygraph. The subjects were asked to describe the pain quality immediately after each drug concentration.

Propofol (Diprivan: propofol 56×10^{-3} mol litre^{-1} in 10% Intralipid) was diluted with either 5% glucose (oil:propofol ratio constant 10:1) or 10% Intralipid (oil:propofol ratio doubled with each degree of dilution) to yield propofol concentrations of 56, 28, 14, 7, 3.5, and 0.0×10^{-3} mol litre^{-1} (pure diluents) and perfused at 35 °C (the temperature of blood in superficial hand veins).

Each subject was studied twice on different days separated by 1–3 weeks. On one day, propofol was used with 5% glucose; on the other, 10% Intralipid was diluent. To avoid long-term alteration of the sensory structures of the vein wall, the same vein segment was not used twice.

Constant i.v. perfusion

After blood was washed out with saline, solutions with different propofol concentrations were perfused constantly (1.5 ml min^{-1}) through the isolated vein segment for 10 min and thereafter rinsed with isotonic saline for 5 min. The various concentrations were studied in randomized sequence. The subjects were not informed about the propofol concentration or about the onset or termination of perfusion and rinsing periods.

Intracutaneous injections

Propofol (0.1 ml of different concentrations) was injected intracutaneously via a 28-gauge steel cannula into marked areas of the hairless skin of the forearm; the propofol concentrations were administered randomly and the subject did not know the actual concentration used. Skin sensation in the marked areas was tested by pinprick, touch, heat and cold at 5, 10 and 20 min after injection.

Data analysis

The time course in pain intensity was evaluated in terms of latency and duration of pain after intracutaneous injections and of latency and time to recovery during rinsing in the i.v. perfusion experiments.

Concentration–pain intensity relations were plotted for each subject by relating the propofol concentrations to the maximal pain for both the injection and perfusion experiments.

Differences in maximal pain for the two dilutions were tested for significance by analysis of variance (repeated measurement ANOVA) followed by Wilcoxon's test; significance was accepted at $P < 0.05$.

RESULTS

Propofol evoked pain in a concentration-related manner in six of eight subjects during perfusion of isolated vein segments and in all eight subjects after intracutaneous injections.

Regardless of the site of application, pain occurred earlier and lasted longer with increasing concentrations of propofol (table I).

There was considerable interindividual variability in the time course of pain. With i.v. perfusion, latency was 9–55 s and time to recovery 42–283 s after application of pure Diprivan. For both i.v. and intracutaneous application, pain intensities increased with the concentration of propofol and, at a given concentration, were always greater with glucose than with Intralipid as diluent (fig. 1). After i.v. application (data from six subjects who experienced pain during perfusion), pain occurred with propofol 3.5×10^{-3} mol litre^{-1} (5 % of the visual analogue scale on the average) with glucose but with propofol 14×10^{-3} mol litre^{-1} (4 % of the visual analogue scale on the average) when Intralipid was diluent. With both diluents, pain intensities increased with the concentration of propofol, to a mean maximum of 60 % (range 20–92 %) of the visual analogue scale at 56×10^{-3} mol litre^{-1} (undiluted Diprivan).

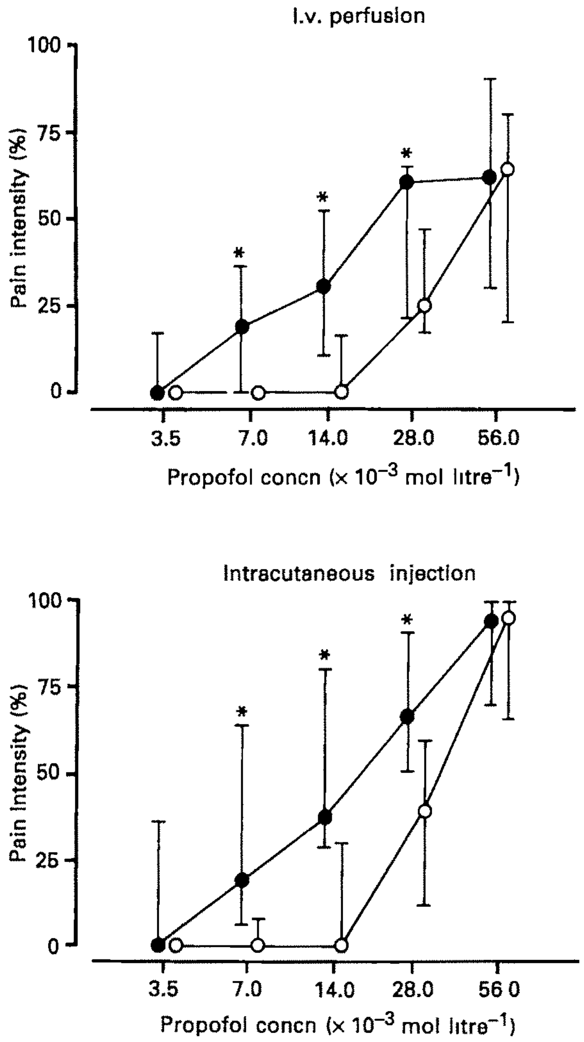

FIG. 1. Effect of propofol concentration on maximum pain (medians and ranges) measured on a visual analogue scale during i.v. perfusion ($n = 6$) and intracutaneous injection ($n = 8$). ○ = dilution of Diprivan with Intralipid; ● = dilution of Diprivan with 5 % glucose. $*P < 0.05$.

Similar results were obtained with intracutaneous injections, which evoked pain in all eight subjects. Pain occurred with propofol 3.5×10^{-3} mol litre^{-1} (6 % of the visual analogue scale) in glucose and with propofol 7.0×10^{-3} mol litre^{-1} (1 % of the visual analogue scale) with Intralipid as diluent. With increasing concentration of propofol, pain increased also, but to a greater degree than during i.v. perfusion; it reached a maximum of 89 % (range 66–100 %) of the visual analogue scale with undiluted Diprivan.

Regardless of the site of application, dilutions of Diprivan with Intralipid evoked significantly less pain than those with 5 % glucose. It should be noted that the diluents never elicited pain. After intracutaneous injections, all subjects noted changes in skin sensitivity over the site of injection which developed within 5 min. They experienced pinprick and warm stimuli as more intense in the presence than in the absence of propofol, although they did not feel cold and touch sensations. These effects occurred only with painful concentrations of propofol, but never with Intralipid or glucose alone. Skin sensitivity returned to normal in all subjects within 20 min. The evoked pain was described as burning and oppressive during i.v. perfusion and mainly as burning after intracutaneous injection.

All subjects suffered from minor venous sequelae such as hypersensitivity to touch and perivascular oedema and flush for several hours. In five of eight subjects, the vein segments became indurated for up to 3 weeks, but thereafter regained normal appearance and function.

After intracutaneous injection of the drug, a rapid flush developed round the site of application, but no long term sequelae occurred.

DISCUSSION

The results of this study suggest that the pain induced by i.v. and intracutaneous administration of propofol is a function of the drug itself rather than the formulation. The pain induced was related to the aqueous concentration of propofol, as shown by the lesser degree of pain induced by dilutions of Diprivan with Intralipid compared with those with 5% glucose.

The isolated vein technique for investigating the mechanisms of induction of pain on i.v. injection of drugs has several advantages. The i.v. concentration of propofol could be maintained constant in the absence of protein binding, dilution and buffering by blood. The exposure time of 10 min should have been sufficiently long for a highly lipophilic agent such as propofol to establish a concentration equilibrium across the intima to the venous nociceptors [6].

Propofol evoked pain in six of eight subjects during i.v. perfusion, but with latencies of up to 55 s—that is, over time periods when patients have usually lost consciousness after i.v. injection. This is in accord with the increase in incidence and intensity of pain after slow injection of propofol [7].

Dilution of Diprivan with Intralipid may be a useful addition to other means advocated for reducing pain on injection, such as the use of a large diameter vein [7], prior administration of aspirin or opioids [8, 9], addition of local anaesthetic drugs [7, 9–12] or cooling [13].

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COMPARISON OF ARTERIAL AND ARTERIALIZED VENOUS CONCENTRATIONS OF PROPOFOL DURING INFUSION OF PROPOFOL

R. W. OKELL, W. W. MAPLESON AND M. D. VICKERS

SUMMARY

Seven patients received a series of low-dose propofol infusions designed to produce three successive pseudo-steady states of arterial blood concentration: 0.06, 0.17 and 0.43 μg ml^{-1}. Arterial and arterialized venous blood samples were obtained simultaneously at the end of each infusion. The results indicate that 95% of the arterialized venous concentrations may be expected to lie within 1±43% of the corresponding arterial concentration, or −5±35% if one set of measurements with poor agreement between duplicate aliquots is omitted.

KEY WORDS

Anaesthetics, intravenous: propofol infusion Monitoring: arterial concentration of drug.

In order to study the physiological effect of an i.v. anaesthetic agent it may be necessary to determine the arterial concentration of the agent. However, for purely research purposes, arterial puncture is avoided where possible because of increased morbidity compared with venepuncture. Major and colleagues [1] found that, after the initial mixing period following a bolus injection, there was no significant difference between arterial, central venous, and peripheral venous concentrations of propofol. However, 4 min after the bolus, the correlation coefficient between arterial and peripheral venous concentrations was only 0.75; therefore, a knowledge of the peripheral venous concentration would account for only 0.75^2 (about 50%) of the variation in the arterial concentration.

Previous studies from this Department, have shown that it is possible, if certain conditions are fulfilled, to use measurements of arterialized venous blood to estimate arterial carbon dioxide tension [2] and halothane concentration [3]. This study was designed to investigate if measurement of the concentration of propofol (Diprivan) in arterialized venous blood may be used to estimate the arterial concentration of propofol during continuous infusion of propofol, when the infusion regimen is designed to produce a subanaesthetic arterial concentration.

PATIENTS AND METHOD

The study was approved by the local research Ethics Committee and written informed consent obtained from all patients. Adult patients undergoing neurosurgical procedures, for which invasive monitoring was indicated, were invited to participate. Patients with renal or hepatic dysfunction or sensitivity to propofol were excluded. Seven patients were recruited to the study. During stable neurosurgical anaesthesia with nitrous oxide, isoflurane, vecuronium and alfentanil, the patients received a bolus and a series of infusions of propofol calculated on the basis of a computer simulation [4], using the data of Gepts and colleagues [5], to produce three pseudo-steady states (table I).

The infusions were delivered by an Ohmeda 9000 syringe pump, in the sequence shown in table I. At the end of each predicted "plateau" of concentration, samples of arterial and arterialized venous blood were drawn simultaneously. Each sample was divided into two aliquots to produce a set of four aliquots at each of three predicted concentrations in each of the seven patients.

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TABLE I. *Sequence of administration of propofol to produce three pseudo-steady states.* † *Predicted arterial concentration at end of infusion*

Infusion	Duration (min)	Dose (mg kg^{-1} h^{-1})	Predicted concn† (µg ml^{-1})
(Bolus)	—	(0.03 mg kg^{-1})	
1st	25	0.25	0.06
Loading	5	1.0	
2nd	20	0.6	0.17
Loading	5	2.3	
3rd	20	1.5	0.43

TABLE II. *Measured concentrations of propofol at the end of each infusion period. Art. venous = arterialized venous*

Patient No.	Infusion	Concentrations (µg ml^{-1}) Art. venous		Arterial	
1	1	0.06	0.06	0.08	0.12
	2	0.14	0.16	0.17	0.17
	3	0.18	0.26	0.36	0.31
2	1	0.11	0.11	0.09	0.10
	2	0.15	0.21	0.20	0.23
	3	0.54	0.42	0.78	0.68
3	1	0.20	0.18	0.16	0.17
	2	0.38	0.37	0.40	0.40
	3	1.07	0.91	0.49	0.59
4	1	0.13	0.09	0.15	0.13
	2	0.09	0.04	0.03	0.03
	3	0.40	0.53	0.78	0.85
5	1	0.30	0.18	0.20	0.18
	2	0.42	0.50	0.41	0.46
	3	0.80	0.76	0.93	0.88
6	1	0.14	0.11	0.10	0.12
	2	0.24	0.29	0.23	0.25
	3	0.62	0.73	0.62	0.64
7	1	0.24	0.22	0.33	0.21
	2	0.31	0.44	0.50	0.62
	3	0.85	0.73	0.76	0.97

Arterialized venous samples were drawn from a 16-gauge cannula (o.d. 1.63 mm) inserted into the dorsum of the hand, without using a tourniquet. The hand was positioned at the level of the heart. Core temperature was monitored using an oesophageal temperature probe and skin temperature using a thermocouple taped to the skin. An electric warming pad was wrapped around the forearm and adjusted to maintain skin temperature approximately 1 °C above core temperature. The tape and the fleece covering of the warming pad were considered sufficient to ensure that the thermocouple registered skin temperature and not blanket temperature. Arterial samples were taken from a 20-gauge radial artery cannula (o.d. 0.91 mm). Propofol was not infused into the arm from which arterialized venous samples were taken.

The samples were mixed immediately with potassium oxalate and stored at 4 °C. Propofol concentrations were measured by the Department of Anaesthetics, University of Bristol, using high pressure liquid chromatography according to the method of Plummer [6]. The coefficients of variation reported by Plummer for the concentrations found in this study were 1.3–5.5% within batches and 8.0–12.3% between batches. The storage phials for the 84 aliquots were prenumbered, in a unique but haphazard manner, so that the person performing the analysis was blind to the pairing of the duplicate aliquots. These duplicates therefore provided the means of determining the coefficient of variation of the analysis in this study.

Statistical analysis was by analysis of variance using Genstat V, Release 4.04B [7] and regression analysis using GLIM 3.12 [8], with P values and correlation coefficients calculated in Minitab Release 5.1.3 [9], all running on a Honeywell mainframe computer under the Multics operating system release 11.

RESULTS

Twenty-one sets of aliquots were obtained from seven patients, each receiving three rates of infusion. The samples covered a range of measured arterial concentrations from 0.03 to 0.93 µg ml^{-1} (table II).

Within each set of aliquots, measurements were expressed as a percentage of the mean of the duplicate arterial aliquots because this led to variances which, apart from two outliers, were about the same for each infusion. This is illustrated in figure 1, in which the mean arterialized venous to mean arterial differences are plotted against predicted concentration. The figure also shows that there was a wide scatter.

Analysis of variance was used to distinguish three sources of variation: between sets of aliquots, between blood vessels within sets, and between aliquots within vessels (the analytical error). The variation between vessels was partitioned into a systematic effect (the mean arterialized venous to arterial difference) and a random

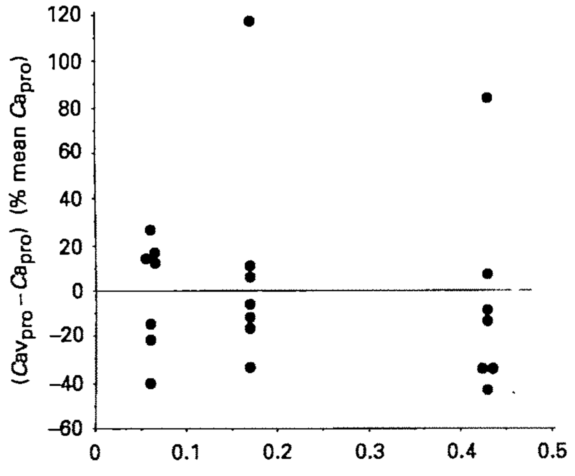

FIG. 1. Scatter of arterialized venous (Cav_{pro}) minus arterial (Ca_{pro}) differences in propofol concentration with each infusion regimen. (Where points overlap, they have been slightly offset from the true predicted concentration.)

variation (table III). The mean difference, +0.8%, was not significant ($F = 0.02$; d.f. = 1, 42; $P = 0.9$); the random variation between vessels was much more than could be explained by analytical error ($F = 2.84$; d.f. = 20, 42; $P < 0.01$). Further analysis of variance demonstrated that there was no significant difference between infusions and no vessel–infusion interaction.

From the mean squares in table III, the SD between aliquots (the analytical error) can be estimated [10] to be $\sqrt{535} = 23\%$ of the arterial mean, and the SD between vessels (after allowing for the contribution from analytical error) can be estimated to be $\sqrt{\{(1518-535)/2\}} = 22\%$ of the arterial mean.

Therefore, although the mean difference between vessels was small, the range of arterialized venous to arterial differences was large. If each is expressed as a percentage of the corresponding mean arterial concentration, the 95% reference interval [11] may be estimated to be $+0.8\% \pm 1.96 \times 22\% = +0.8 \pm 43\%$. In other words, if an arterialized venous sample is analysed, in addition to the uncertainty arising from the analytical error, its concentrations may (with 95% probability) be between 42% less than the true arterial concentration and 44% greater.

DISCUSSION

The variability of the present results (±43% compared with ±18% in the similar study of halothane concentrations [3]) is surprising. Good arterialization was thought to have been achieved in all patients; but perhaps the arterial concentration at the time of sampling was not as steady as the computer simulation predicted. This question could be answered by repeating the study with several arterial samples being drawn in the last 5 min of each plateau to test the steadiness of the concentration. In the meantime, it is worth noting that the measured concentrations did not agree closely with the predicted values (fig. 2). Regression analysis showed that the data could be represented adequately by a set of straight lines through the origin with slopes of 0.9–3.1, mean 1.68, with a 95% confidence interval for the mean of 1.1–2.5. (The analysis was made in terms of log concentration in order to obtain consistent variances and the results were converted back to linear terms.)

An SD between aliquots of 23% is much more than the coefficient of variation reported [6] for the Plummer method (up to 12.3%). A somewhat similar difference was found in the earlier study of halothane concentrations [3]: there the SD between aliquots was 5.1%, whereas the original account

TABLE III. *Analysis of variance of measured concentrations expressed as a percentage of the mean arterial concentration for each set of aliquots*

Source of variation	Sums of squares	d.f.	Mean square	Variance ratio	P
Between sets of aliquots (random)	30366	20	1518		
Between vessels within sets					
Systematic	13	1	13	0.01	0.9
Random	30366	20	1518	2.84	0.02
Between aliquots within vessels (random)	22467	42	535		
Total	83212	83			

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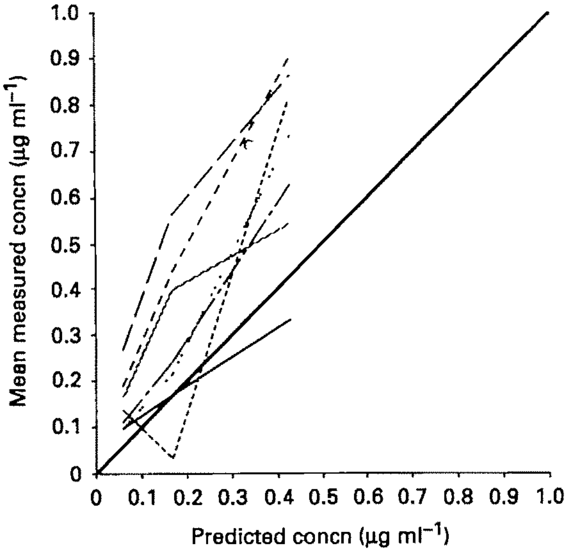

FIG. 2. Relationship between mean measured and predicted arterial concentrations. The thick continuous line is the line of identity.

of the analytical method used [12] reported a variability corresponding to an SD up to only 1.7%. This illustrates the value of analysing duplicate aliquots as a check on reported reproducibility of an analytical method.

However, inspection of the individual results reveals that one set of aliquots, corresponding to the highest point in figure 1, was unusual in three respects: it had concentrations which were much smaller than predicted; it had the smallest mean concentration (0.05 μg ml^{-1}) of all sets; and there was poor agreement between the two arterialized venous aliquots. If this set is omitted, the SD between aliquots decreases to 15%, the SD between vessels becomes 18%, and the mean arterialized venous concentration becomes 5% less than the mean arterial concentration. On this basis, 95% of the arterialized venous concentrations can be expected to lie within -5 ± 35% of the corresponding arterial concentration.

An SD of 15% between aliquots is probably a fairer estimate of the analytical error than 23%; but the conclusion seems inescapable that, at least at these low concentrations, measurement of arterialized venous concentration is of very limited value in estimating the arterial concentration in an individual patient. However, it may be acceptable for mean concentrations measured in substantial numbers of patients for research purposes.

Major and colleagues [1] reported their results in terms of the correlation coefficient (0.75) between arterial and peripheral venous concentrations. In the present study, the correlation coefficient between arterial and arterialized venous concentrations was 0.835. It seems likely, therefore, that ordinary peripheral venous samples would provide even less reliable estimates of arterial concentrations of propofol. Incidentally, this is another demonstration that a "high" correlation coefficient between two variables does not indicate that one is a good predictor of the other.

This study was undertaken because of an interest in the effect of low concentrations of propofol, but the results are of relevance when following concentrations well into recovery from clinical doses.

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NEUROMUSCULAR AND CLINICAL EFFECTS OF MIVACURIUM CHLORIDE IN HEALTHY ADULT PATIENTS DURING NITROUS OXIDE–ENFLURANE ANAESTHESIA†

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SUMMARY

We have studied the effects of mivacurium after induction of anaesthesia with alfentanil–propofol in healthy adult oral surgical patients. Anaesthesia was maintained with nitrous oxide and 0.75% (end-tidal) enflurane in oxygen after nasotracheal intubation. Recordings were made of the rectified compound adductor pollicis electromyogram in response to train-of-four (TOF) ulnar nerve stimulation. First and fourth TOF responses were defined as T1 and T4, with T1 suppression referenced to pre-mivacurium T1 height (Tc). Onset times (mean (SEM)) to 90% T1 suppression were 2.5 (0.2), 2.1 (0.3) and 1.6 (0.1) min, respectively, after mivacurium 0.15 mg kg^{-1} (n = 18) and 0.2 mg kg^{-1} (n = 18) as 5-s boluses and 0.2 mg kg^{-1} over 30 s (n = 9). Intubating conditions 2 min after 0.15 mg kg^{-1} were good to excellent and not improved by a further 30-s delay or by use of a 0.2-mg kg^{-1} dose. Recovery to T1/Tc of 5% occurred on average in 12–13 min irrespective of dose. Thereafter, mivacurium infusions commenced at 8–10 μg kg^{-1} min^{-1} were adjusted at intervals of at least 3 min to achieve T1/Tc in the range 1–10%. Mean duration of infusion was 58 (3.4) min and mean infusion rate after a 15-min stabilization period was 6.6 (range 2.3–12.9) μg kg^{-1} min^{-1}. On cessation of infusions, spontaneous recovery from T1/Tc 8% (1.0%) to T4:T1 = 0.7 took 17 (1.2) min. Neostigmine 0.04 mg kg^{-1} or edrophonium 0.75 mg kg^{-1} evoked recovery from T1/Tc 9% (SEM 1.2% and 1.0%, respectively) to T4:T1 = 0.7 in 11 (0.6) and 8 (0.9) min (both $P < 0.001$ vs spontaneous recovery).

KEY WORDS

Neuromuscular relaxants: mivacurium.

Mivacurium chloride (BW B1090U) is a new non-depolarizing neuromuscular blocking agent. Previous clinical trials in the United States [1–9] have shown that it has a shorter duration of action than currently approved non-depolarizing agents and may be suitable for providing neuromuscular block for procedures of brief duration when suxamethonium is not desired, and for maintenance of neuromuscular block by infusion.

We have assessed onset times and conditions at tracheal intubation after fast bolus administration of mivacurium. A slow bolus injection group was included also, as mivacurium may be associated with cutaneous flushing and arterial hypotension caused by systemic release of histamine [8]. Infusion requirements were ascertained under anaesthesia with nitrous oxide and enflurane, and the time for spontaneous recovery of neuromuscular function was compared with that achieved after neostigmine or edrophonium.

PATIENTS AND METHODS

The study was approved by the Committee on Safety of Medicines and the local Ethics Committee. Forty five patients requiring nasotracheal intubation for elective oral surgical procedures gave written informed consent. They were of physical status ASA I or II, and not taking antihistamines or medications known to affect neuromuscular function. Premedication 60–

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90 min before induction of anaesthesia consisted of oral atropine 1 mg and temazepam 20–30 mg. Electrocardiographic and non-invasive arterial pressure monitoring (Datascope Accutorr) commenced in the anaesthetic room. Adhesive, pre-jelled silver–silver chloride surface electrodes were positioned on the wrist and hand, and connected to a Datex Relaxograph in order to detect the evoked gated integrated rectified compound electromyographic (EMG) response of the adductor pollicis muscle to supramaximal train-of-four (TOF) ulnar nerve stimulation (0.1-ms square-wave stimuli at 2 Hz for 2 s; train frequency 0.05 Hz). The hand from which EMG recordings were obtained was immobilized with the thumb abducted, and the arm was wrapped in cotton wool to minimize heat loss. Palmar and core temperatures were monitored with skin and nasopharyngeal probes.

After i.v. induction of anaesthesia with alfentanil 0.5–1.0 mg and propofol 2.0–2.5 mg kg^{-1}, a stable baseline EMG recording was obtained. Rectified EMG output from the Relaxograph was recorded continuously on a Gould 220 chart recorder for later analysis. The height of the first response (T1) of the TOF at baseline was defined as the control response (Tc). Before tracheal intubation, anaesthesia was maintained with 66 % nitrous oxide in oxygen, and increments of alfentanil and propofol as clinically indicated. Mivacurium 2 mg ml^{-1} was administered at least 2 min after the last increment of alfentanil or propofol.

Patients were studied in three groups. The first 18 patients (group A) were allocated randomly to receive an initial dose of mivacurium 0.15 mg kg^{-1} (subgroup A1) or 0.2 mg kg^{-1} (subgroup A2) as a rapid, 5-s bolus via a peripheral vein, and tracheal intubation was attempted 2.5 min later. The next 18 patients (group B) were similarly allocated randomly to receive mivacurium 0.15 mg kg^{-1} (subgroup B1) or 0.2 mg kg^{-1} (subgroup B2) by rapid, 5-s bolus, but with tracheal intubation 2 min after the injection of mivacurium. The final nine patients (group C) received mivacurium 0.2 mg kg^{-1} over 30 s, with tracheal intubation attempted 2 min later. Intubating conditions were graded on an interval scale from 1 = excellent to 4 = not possible, according to the observed state of relaxation of the vocal cords and the severity of coughing or passing the tracheal tube. After successful tracheal intubation, enflurane was added to the inspired gases to achieve an end-tidal concentration of 0.75 % (Datex Normac) and ventilation was controlled to maintain an end-tidal partial pressure of carbon dioxide 4.4–5.4 kPa (Datex Normocap). Nasopharyngeal and palmar temperatures were maintained greater than 35 °C and 33 °C, respectively.

All patients received an infusion of mivacurium 0.5 mg ml^{-1} in 5 % glucose to extend neuromuscular block for the duration of surgery. Infusions were commenced after EMG recovery from the initial bolus of mivacurium was evident ($T1/Tc > 5\%$). An initial infusion rate of 10 μg kg^{-1} min^{-1} was used in the first nine patients studied, but in subsequent patients this was modified to 8 μg kg^{-1} min^{-1}. The rate was then adjusted by increments of 1 μg kg^{-1} min^{-1} at intervals of at least 3 min to achieve and maintain T1/Tc in the range 1–10 % (90–99 % T1 suppression). Infusions were administered using a Ohmeda 9000 syringe pump and a dedicated i.v. cannula.

Towards the end of surgery the infusion was discontinued and group B patients allowed to recover spontaneously from the effects of mivacurium. Residual neuromuscular block was antagonized with neostigmine 40 μg kg^{-1} and atropine 20 μg kg^{-1} in group A patients, and with edrophonium 750 μg kg^{-1} preceded by atropine 10 μg kg^{-1} in group C patients. EMG monitoring was continued until the T4:T1 ratio (the ratio of the height of the 4th response (T4) of the TOF to T1) reached at least 0.7. Anaesthesia was discontinued and, after spontaneous ventilation was established, the trachea was extubated.

For each patient, the times from bolus injection to 90 % and to maximal T1 suppression, T1 suppression at intubation, intubation scores and times for initial recovery of T1/Tc to 5 % and 10 % were noted. (All times were from completion of injection of mivacurium.) Changes in infusion rate, mean infusion rate and infusion duration were recorded. After infusions, T1/Tc at antagonism (groups A and C) or at cessation of infusion (group B) was noted, and the time for recovery to T4:T1 ratios of 0.5 and 0.7 recorded. Patient data were analysed with one-way analysis of variance (ANOVA). Neuromuscular data were analysed using one-way ANOVA, Student–Newman–Keuls test, and Bonferroni *t* tests as appropriate. Chi square was used to analyse intubation scores. $P < 0.05$ was considered statistically significant.

Non-invasive cardiovascular monitoring was performed according to normal anaesthetic prac-

Table I. *Details of patients and total doses of propofol and alfentanil given before the initial attempt at tracheal intubation (mean (SD))*

Group or subgroup	Weight (kg)	Age (yr)	Height (cm)	Sex (M:F)	Propofol (mg kg^{-1})	Alfentanil (μg kg^{-1})
A1	66.3	28.3	165.8	3.6	2.91	14.8
	(14.2)	(9.3)	(9.2)		(0.52)	(3.3)
A2	68.7	26.7	167.7	3:6	3.90	15.7
	(14.3)	(6.6)	(9.7)		(1.49)	(4.8)
B1	71.8	27.8	174.2	6:3	2.72	17.1
	(9.4)	(6.0)	(8.4)		(0.67)	(3.3)
B2	73.6	26.2	171.7	5:4	3.20	13.9
	(11.1)	(4.0)	(9.2)		(0.27)	(1.9)
C	64.0	28.2	168.4	3:6	3.61	15.3
	(7.3)	(10.0)	(5.8)		(1.11)	(1.8)

Table II. *Onset of block (mean (SEM) [range]). Times are taken from the end of mivacurium injection.* †n = *17*; ‡n = *15. Rapid bolus dose = 5 s; slow bolus dose = 30 s.* *P < *0.05*

Dose (mg kg^{-1})	Time to % T1 suppression (min)		Time to % T1 recovery (min)	
	90%	Maximal	5%	10%
0.15 Rapid	2.5 (0.2)	3.7 (0.3)*	11.5 (0.9)	†12.8 (0.8)
(n = 18)	[1.6–3.7]	[1.7–6.0]	[5.9–18.7]	[7.9–20.4]
0.20 Rapid	2.1 (0.3)	2.6 (0.3)	†12.7 (0.9)	‡14.2 (0.9)
(n = 18)	[0.8–4.4]	[1.1–5.1]	[8.5–19.9]	[9.5–22.1]
0.20 Slow	1.6 (0.1)*	2.4 (0.2)	13.3 (0.8)	15.0 (0.9)
(n = 9)	[1.2–2.7]	[1.8–3.1]	[8.5–16.9]	[10.5–19.6]

tice. Clinical signs of histamine release, such as cutaneous flushing were documented. In addition, arterial pressure (AP) and heart rate (HR) were recorded immediately before and every 1 min for 10 min after the initial dose of mivacurium. Baseline AP and HR were defined as values immediately preceding administration of mivacurium. In order to avoid the compounding haemodynamic effects of tracheal intubation, analyses were made only of the maximum change in HR and mean arterial pressure (MAP) from baseline observed in the period after mivacurium but before tracheal intubation. Paired *t* tests and Fisher's Exact tests were used to analyse these changes and significance taken at $P < 0.05$.

RESULTS

Patient groups were comparable with respect to weight, age, height and total doses of propofol and alfentanil received before the initial attempt at tracheal intubation (table I). There were no significant differences between patients who received initial 5-s boluses of mivacurium 0.15 mg kg^{-1} (subgroups A1 and B1) or 0.2 mg kg^{-1} (subgroups A2 and B2).

There were no significant differences in onset and early recovery data between subgroups that received identical initial mivacurium doses over 5 s; such data were analysed in combination and are summarized in table II. Mean onset times (from end of injection) to 90 % and to maximal T1 suppression after mivacurium 0.15 mg kg^{-1} were slower than those after 0.2 mg kg^{-1}, although the difference in times to 90 % suppression between the two doses when administered over 5 s was not statistically significant. T1 suppression of 100 % was produced in all but two patients; one reached 97 % suppression after a dose of 0.15 mg kg^{-1}, and another achieved maximal T1 suppression of only 90 % after mivacurium 0.2 mg kg^{-1} administered over 5 s.

Data from three patients in whom oral tracheal intubation was performed (n = 1) or unexpectedly difficult insertion of the tracheal tube through the nasal passage was encountered (n = 2) were ex-

TABLE III. *Tracheal intubation data (mean* (SEM) *[range]). Intubation scores: 1 = excellent (easy passage of tube, no cough, cords relaxed); 2 = good (slight cough/buck, cords relaxed); 3 = poor (moderate cough/buck, cords moderately adducted); 4 = not possible (cords tightly adducted). Times are from completion of mivacurium injection. Rapid bolus dose = 5 s; slow bolus dose = 30 s*

Group or subgroup	Mivacurium dose (mg kg^{-1})	Time of attempt (min)	T1 suppression at attempt (%)	Intubation score 1	2	3	4
A1	0.15 Rapid	2.5	87.8 (3.7) [72–100]	4	3	0	2
B1	0 15 Rapid	2.0	72.4 (8.2) [36–100]	2	5	0	0
A2	0.20 Rapid	2.5	88.1 (7.3) [42–100]	6	2	1	0
B2	0.20 Rapid	2 0	91 9 (2 8) [75–100]	3	4	0	1
C	0.20 Slow	2.0	94.3 (1.4) [87–100]	5	4	0	0

cluded from analyses of intubation scores. Data from the remaining patients are summarized in table III. Intubating conditions were generally good to excellent 2 or 2.5 min after mivacurium 0.15 mg kg^{-1}; whilst in two patients the trachea could not be intubated at 2.5 min, all patients given this dose in whom tracheal intubation was attempted at 2 min displayed at least good conditions. The two patients presented early in the study, and inexperience may have been partly responsible for the failures. Mean T1 suppression at 2 min after mivacurium 0.15 mg kg^{-1} was 72%—less than that at 2.5 min in comparable patients given the same dose (88%). Mean T1 suppression was greater in patients given mivacurium 0.2 mg kg^{-1} compared with those who received the lesser dose, but no significant benefit in terms of superior intubating scores was demonstrated. Slowing the rate of injection of a 0.2-mg kg^{-1} dose did not influence conditions at 2 min, although it should be stressed that timings were taken from completion of injection.

Mean times from administration of the mivacurium bolus to 5% and 10% T1 recovery were 11–13 min and 13–15 min, respectively, with no significant relation to dose or to initial speed of administration (table II). One patient did not achieve sufficient T1 suppression to be included in these recovery times, and in another three patients the mivacurium infusion was started after recovery to T1 of 5%, but before recovery to 10%.

There was no discernible bolus dose or group related differences in infusion data, which were pooled, therefore, for all patients (table IV). Over the first 15 min, regular changes in infusion rates were generally necessary. After this time, infusion rates usually remained stable (fig. 1), although 1-µg kg^{-1} min^{-1} changes in infusion rate to correct drift outside the target T1/Tc range occasionally resulted in temporary overcorrection. Mean infusion rate for all patients in the period after the 15-min stabilization was 6.6 µg kg^{-1} min^{-1} (range 2.3–12.9 µg kg^{-1} min^{-1}). There was a negative trend between individual times from initial bolus administration of mivacurium to 5% T1/Tc recovery and post-15 min infusion rates (fig. 2); whilst tests for equality of slopes of regression lines failed to demonstrate significant differences related to size of initial dose, pooled regression analyses were felt to be inappropriate.

TABLE IV. *Infusion data (mean* (SEM) *[range]) combined for all patients except: *excludes data from two patients in whom duration of infusion was < 15 min*

T1 suppression at start of infusion (%) ($n = 45$)	81.8 (1.7) [45–92]
Mean duration of infusion (min) ($n = 45$)	57.8 (3.4) [10–121]
Mean infusion rate first 15 min (µg kg^{-1} min^{-1}) ($n = 43$)	8.4 (0.2)* [6.2–11 3]
Mean infusion rate after 15 min (µg kg^{-1} min^{-1}) ($n = 43$)	6.6 (0.4)* [2.3–12.9]

On termination of infusions, mean T1/Tc, and T1/Tc ranges at the time of administration of anticholinesterase were similar in group A and group C patients, and comparable to those at termination of infusion in group B patients in whom spontaneous recovery was allowed (table V). Occasional patients in all three groups were

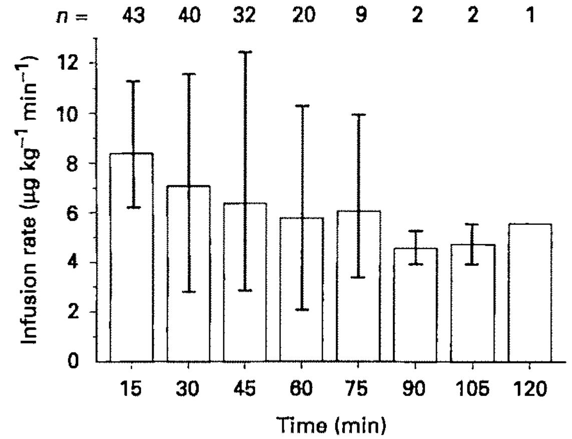

FIG. 1. Mean infusion rates and ranges for all patients at 15-min epochs from the start of the mivacurium infusion. Infusion rate data for individual patients were included for each epoch only if such data extended to the conclusion of that epoch.

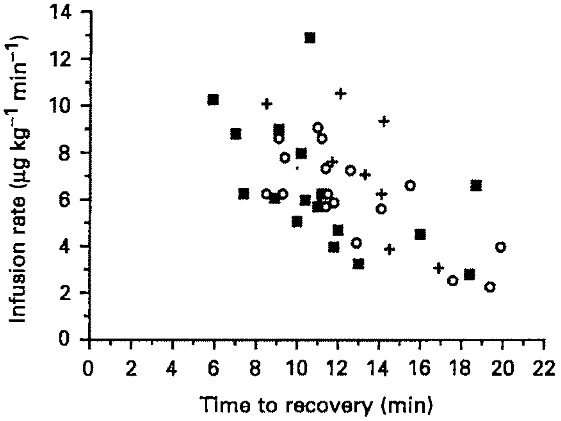

FIG. 2. Mean individual infusion rates from 15 min after commencement of mivacurium infusions plotted against the time to 5% T1/Tc recovery following bolus doses of mivacurium. ■ = 5-s bolus of mivacurium 0.15 mg kg^{-1}; ○ = 5-s bolus of 0.2 mg kg^{-1}; + = 30-s bolus of 0.2 mg kg^{-1}.

outside the 1–10% T1/Tc range at the time of termination of infusion, for the reason mentioned above. Spontaneous recovery was fairly rapid and often evident to a small degree before administration of anticholinesterase. Compared with spontaneous recovery, both anticholinesterases significantly increased the speed of recovery. A T4:T1 ratio of 0.7, but not 0.5, was reached significantly more rapidly in patients given edrophonium compared with those who received neostigmine. No patient manifested signs of muscle weakness in the recovery area when assessed by 5-s head lift and hand grip.

Mean maximum changes in MAP from baseline observed after initial injection of mivacurium but before tracheal intubation were decreases of 0.9 (SD 7.6), 6.3 (8.5) and 5.3 (10.5) mm Hg in patients who received mivacurium 0.15, 0.2 (rapid), and 0.2 (slow) mg kg^{-1}, respectively. Corresponding mean maximum increases in HR were 1.7 (SD 5.9), 4.7 (12.7) and 6.9 (12.6) beat min^{-1}. These changes bore no significant relation to dose or to speed of administration and were not significant deviations from mean baseline values. Decreases in MAP > 20% of baseline were observed in one of 18 patients (6%) who received a rapid 0.15-mg kg^{-1} bolus, compared with five of 18 (28%) and three of nine (33%) patients after a rapid or slow 0.2-mg kg^{-1} dose, respectively ($P > 0.05$). There was no difference relating to dose or to speed of administration in the incidence of flushing (five of 18 patients after mivacurium 0.15 mg kg^{-1}; six of 18 after rapid 0.2 mg kg^{-1}; three of nine after 0.2 mg kg^{-1} over 30 s). No other untoward perioperative events attributable to mivacurium were observed.

TABLE V. *Recovery data (mean (SEM) [range]). Group A patients received neostigmine 40 µg kg^{-1}; group B patients allowed to recover spontaneously; group C patients received edrophonium 750 µg kg^{-1}. †T1 at cessation of infusion. Significant differences:* *P < 0.05 *compared with neostigmine;* ***P < 0.001 *compared with spontaneous recovery*

Group	*n*	Recovery type	T1 recovery at reversal (%)	Time to T4:T1 ratio (min)	
				0.5	0.7
A	18	Neostigmine	9.1 (1.2) [3–22]	7.6 (0.5)*** [4.9–12.4]	11.2 (0.6)*** [7.2–17.8]
B	18	Spontaneous	7.8 (1.0)† [1–16]	13.8 (1.0) [7.2–24.2]	17.1 (1.2) [10.2–29.8]
C	9	Edrophonium	9.0 (1.0) [5–14]	5.8 (0.8)*** [2.1–9.1]	8.2 (0.9)* [4.1–12.1]

DISCUSSION

The doses of mivacurium used (0.15 and 0.2 mg kg^{-1}) were selected as appropriate to facilitate tracheal intubation at 2–2.5 min, and on the basis of published work approximate to 2.0 and $2.5 \times ED_{95}$ estimates during opioid anaesthesia [7]. Larger doses may (with priming) produce favourable intubating conditions at 90 or even 60 s [6], but may not be clinically useful because of untoward cardiovascular effects which are dose-dependent at doses in excess of 0.15 mg kg^{-1} [3, 8]. Enflurane is reported to potentiate the neuromuscular effects of mivacurium [4] and its administration was delayed until after tracheal intubation and the development of 90% T1 suppression.

Thiopentone was the induction agent used in previous studies, whereas our patients received propofol. Our results on onset of block are similar to those reported previously during opioid anaesthesia, with no evidence to suggest that a single bolus dose of propofol alters the action of mivacurium. Whilst it is recognized that ease of tracheal intubation depends on other factors in addition to the degree of neuromuscular block, intubating conditions at 2 min were adequate in most patients after mivacurium 0.15 mg kg^{-1}, with no significant benefit in waiting a further 30 s or in increasing the dose to 0.2 mg kg^{-1}. It may be inappropriate to compare these findings with those of other workers, as tracheal intubation was performed via the nasal route. T1 recovery to 10% of Tc was more than twice as rapid as that reported after vecuronium during enflurane anaesthesia [10], and about twice that after an intubating dose of suxamethonium [2, 3]. It should be stressed, however, that mivacurium was not administered initially during stable enflurane anaesthesia in this study. We were unable to demonstrate any differences in early recovery times between the two doses, which is not very surprising in view of their similarity and the relatively small number of patients studied.

After an initial period of stabilization, infusions of mivacurium provided controllable neuromuscular block for up to 2 h. An initial rate of 10 μg kg^{-1} min^{-1}, advocated previously during opioid anaesthesia [1], proved too great for our patients during enflurane anaesthesia and a lesser initial rate was thus adopted. Our mean infusion rate of 6.6 μg kg^{-1} min^{-1} is almost identical to that during enflurane anaesthesia reported by Caldwell and colleagues [3]. However, as with atracurium and vecuronium [1, 3, 11], we observed a marked (more than five-fold) variation in individual infusion rates. As recovery from mivacurium is largely a result of breakdown by plasma pseudocholinesterase [5], part of this variation may be a result of interpatient differences in activity of this enzyme [1, 7]. Our results may also show that individual sensitivity to mivacurium in terms of longer recovery time after bolus doses may be expressed also as lower infusion requirements, as shown previously [9], but we would hesitate to suggest that recovery time may broadly predict stable infusion rate outside our prevailing study conditions.

When competitive neuromuscular blocking drugs are used, attainment of a T4:T1 ratio of 0.7 is widely believed to equate with clinically adequate recovery [12, 13], although some workers argue that even further recovery is necessary to ensure airway protection [14], especially when using EMG monitoring [15]. We do not yet know if these data are applicable to mivacurium, and elected to use an EMG T4:T1 of 0.7 as the end-point of our neuromuscular monitoring. Spontaneous recovery to a T4:T1 of 0.7 took 17 min, approximately 50% as long as that shown earlier for atracurium under comparable conditions [11]. Whilst edrophonium was shown to be superior to neostigmine in accelerating recovery, no work has yet been performed on the relative potencies of these agents when antagonizing mivacurium-induced block, and the doses used may not have been strictly comparable. No patient demonstrated evidence of inadequate muscle power in the period after attainment of an EMG T4:T1 of 0.7, but subtle alterations in ventilatory mechanics were not evaluated.

In contrast with previous findings after thiopentone–opioid induction [8], we failed to demonstrate any significant differences in AP and HR changes in the period immediately after rapid injection between the two doses used. This may possibly have been the result of our use of propofol at induction, or the use of atropine in premedication. We suggest, however, that a 30% incidence of decreases in MAP $\geqslant$ 20% after mivacurium 0.2 mg kg^{-1}, even with slow injection, may be clinically unacceptable. Cutaneous flushing was noted in approximately 30% of patients, and there was no relationship with dose or speed of injection. In view of the similarity in efficacy between 0.15- and 0.2-mg kg^{-1} doses and the reported haemodynamic effects of greater doses, we conclude that there seems little clinical justification in the use of a dose of mivacurium exceeding 0.15 mg kg^{-1}.

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EFFECTS OF LABETALOL ON PERIOPERATIVE STRESS MARKERS AND ISOFLURANE REQUIREMENTS†

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SUMMARY

We have studied the effect of labetalol on anaesthetic requirements, cardiac and humoral responses in 16 healthy women during elective abdominal surgery. The experimental group ($n = 8$) received increments of i.v. labetalol 0.15–0.3 mg kg^{-1} to reduce mean arterial pressure (MAP) by 15% from values obtained before anaesthesia. All patients received thiopentone 6 mg kg^{-1} and anaesthesia was maintained with isoflurane and nitrous oxide. In the placebo group, tracheal intubation provoked a 33% increase in heart rate (HR) and a 52% increase in MAP ($P < 0.001$ vs baseline for both). In contrast, pretreatment with labetalol resulted in a 7.3% increase in HR and a 21.3% increase in MAP ($P < 0.05$ vs baseline for MAP). Two patients treated with labetalol had a reduction in MAP to 50–60 mm Hg during surgery. After tracheal extubation, the labetalol group had a significantly slower HR than the placebo group ($P < 0.05$). The cardiovascular response to tracheal intubation was associated with an increase in plasma noradrenaline concentration in both groups. Labetalol did not affect isoflurane requirements, plasma concentrations of adrenaline, cortisol and aldosterone or arterial P_{O_2}, but prevented the decrease in plasma concentration of potassium which occurred in placebo treated patients ($P < 0.05$) in early recovery. We conclude that preanaesthetic administration of labetalol attenuated the perioperative hypertensive and tachycardic responses, but was accompanied by intraoperative hypotension when given in doses > 0.5 mg kg^{-1}, despite an increase in plasma noradrenaline concentrations.

KEY WORDS

Anaesthesia: general Anaesthetics, volatile. isoflurane. Hormones: stress response to surgery. Sympathetic nervous system: catecholamines, sympatholytics; labetalol.

It is assumed generally that the cardiovascular changes following laryngoscopy and tracheal intubation represent an adrenergic response [1–5]. Thus it has been proposed that an abrupt increase in circulating plasma concentrations of catecholamines may be associated with potentially severe hypertension and tachycardia which, in turn, may cause cardiac arrhythmias, myocardial ischaemia, left ventricular dysfunction and rupture of cerebral aneurysms [6, 7] in susceptible individuals [8, 9].

Several agents and regimens have been devised to control these transient haemodynamic responses to tracheal intubation. Labetalol, a non-selective β- and α_1-adrenergic blocker, has been used previously to block the haemodynamic responses to tracheal intubation [10–15]. The dose of labetalol used in these studies varied widely. Furthermore, previous studies reported cardiovascular effects during a relatively short period of time (10–20 min) after administration, even though this agent has an elimination half-life of approximately 5–6 h [16]. There is little information on the effect of labetalol on sympathoadrenal responses, arterial oxygenation or plasma concentrations of potassium during anaesthesia, surgery and early recovery.

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PATIENTS AND METHODS

We studied 16 ASA I women undergoing elective intra-abdominal surgery. The study was approved by the local institutional review board and written informed consent was obtained from each patient. Patients with co-existing systemic illness, A–V block or receiving cardiac drugs were excluded. All patients were premedicated with incremental doses of midazolam 0.5 mg i.v. (range 0.03–0.08 mg kg^{-1}) before radial artery cannulation and received lactated Ringers solution 10 ml kg^{-1} over 20–30 min to attenuate hypotension after thiopentone. Monitoring included ECG lead II, pulse oximetry, continuous intra-arterial pressure and end-tidal concentrations of carbon dioxide, oxygen, nitrous oxide and isoflurane (Datex—254 Airway Gas Monitor). Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), MAP and heart rate (HR) were recorded as an average of three separate readings within 1 min. End-expiratory isoflurane concentration was recorded every 15 min from the time of tracheal intubation until extubation.

Patients were allocated randomly to two treatment groups: group I (eight patients) received placebo: i.v. saline 8 ml in divided doses in 12 min; group II (eight patients) received labetalol 0.15 mg kg^{-1} i.v. initially, followed by 0.25–0.3 mg kg^{-1} every 3 min as needed (up to 1 mg kg^{-1} total), to reduce MAP by 15% from baseline values. Cardiovascular measurements and blood collection were performed at 10 time points: baseline; post-titration; post-induction; 1 and 5 min after intubation; 1, 15 and 30 min after incision; tracheal extubation; in the recovery room. Although mean arterial pressure was a controlled variable initially, it was treated as an independent variable after the titration period.

The anaesthetist was blinded as to whether the patient received labetalol or placebo. All patients received vecuronium 15 μg kg^{-1} as a priming dose. Five minutes later, anaesthesia was induced with thiopentone 6 mg kg^{-1} i.v. over 90 s. Vecuronium 0.1 mg kg^{-1} i.v., was given and tracheal intubation was carried out 2 min later. Anaesthesia was maintained with 50% nitrous oxide and isoflurane in oxygen (inspired concentration, determined by an anaesthetist other than the study physician, was titrated to counteract cardiovascular responses to surgery, as is routine practice). After closure of the peritoneum, all patients received fentanyl 1 μg kg^{-1} and droperidol 15 μg kg^{-1}. Neuromuscular block was antagonized with neostigmine 50 μg kg^{-1} and glycopyrronium 8 μg kg^{-1} i.v.

Hormonal assays

All arterial blood samples were centrifuged at −4 °C and stored at −80 °C until the time of analysis. Plasma concentrations of adrenaline and noradrenaline were measured by radioenzymatic assay as described previously [17, 18]. Plasma cortisol concentration was measured by solid phase radioimmunoassay [18, 19]. Plasma renin activity (Angiotensin-J-Biotecx, Friendswood, TX) and plasma concentration of aldosterone (Coat-a-Count Diagnostic Products, Los Angeles, CA) were measured by radioimmunoassay. Serum concentration of potassium was measured by the NOVA 6 (NOVA Biomedical, Waltham, MA) electrolyte analyser. Plasma concentration of labetalol was measured by high pressure liquid chromatography with fluorimetric detection [20]. The intra- and interassay variations, respectively, were 6.2% and 8.0% for adrenaline, 6.4% and 13.3% for noradenaline, 3.7% and 10% for cortisol and < 5% for both renin and aldosterone.

Statistical analysis

Results in the text and figures are reported as mean values (SEM) unless otherwise indicated. Intergroup comparisons of patient data, drug doses, fluids and isoflurane concentrations were performed using Student's *t* test for unpaired data. The dependent variables (cardiovascular responses, plasma concentration of adrenaline, noradrenaline, cortisol, renin, aldosterone and potassium, and arterial P_{O_2}) were assessed by a repeated measures analysis of variance procedure (MANOVA) [21]. All tests of significance were set at an alpha level of 0.05.

RESULTS

There was no significant difference between the two groups in age, weight, duration of surgery and anaesthesia, blood loss and volume of crystalloids given (table I). Total abdominal hysterectomy was performed in nine patients (five given labetalol); ovarian cystectomy was performed in the remaining seven patients (three given labetalol). Midazolam was given i.v. for sedation before the study, in a mean dose of 5.6 (SEM 1.5) mg in the placebo group and 4.6 (0.7) mg in the labetalol group (ns). The end-expiratory concentrations of

TABLE I. *Patient data (mean* (SD) *[range*])

	Placebo group ($n = 8$)	Labetalol group ($n = 8$)
Age (yr)	35.9 (10.3) [24.0–53.0]	43.9 (6.7) [36.0–53.0]
Weight (kg)	70 6 (10.2) [55.0–85.0]	70.0 (15.3) [50.0–100.0]
Duration of surgery (min)	125.6 (50.0) [90.0–230.0]	120.0 (29.7) [90.0–180.0]
Duration of anaesthesia (min)	159.4 (51.8) [120.0–270.0]	160.6 (34.0) [120.0–225 0]
Blood loss (ml)	387.5 (270.9) [150.0–1000.0]	375.0 (134.3) [200 0–625.0]
Crystalloids (ml)	2493.8 (1271.2) [1500.0–5500.0]	2425 0 (426.8) [2000.0–3200.0]

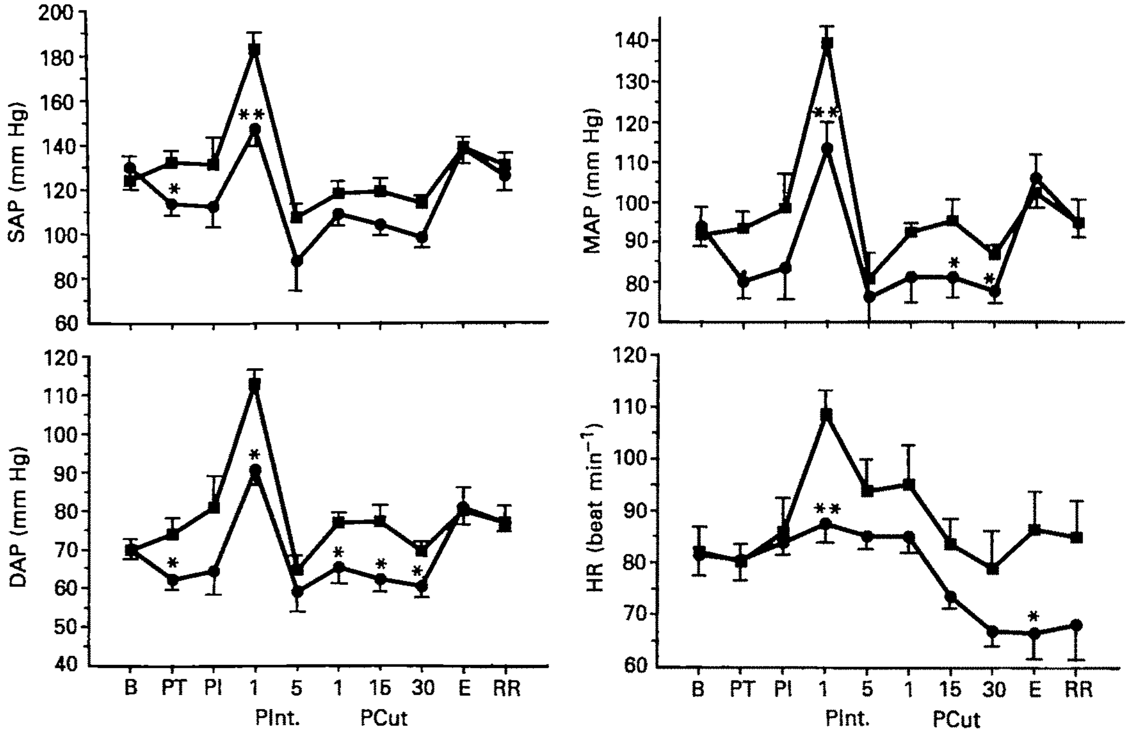

FIG. 1. The mean values (SEM) for heart rate (HR) and arterial pressures (DAP, SAP, MAP) for the labetalol (●) and placebo (■) groups at the 10 time points: B = Baseline; PT = post-titration; PI = post-induction; 1, 5 PInt. = 1 and 5 min post-intubation; 1, 15, 30 PCut = 1, 15 and 30 min post-incision; E = tracheal extubation; RR = recovery room. Differences between groups: $^{*}P < 0.05$; $^{**}P < 0.01$.

isoflurane, during the initial 120 min from the time of tracheal intubation were not statistically different between the two groups.

Cardiovascular responses

Cardiovascular data are shown in figure 1. The titrated dose of labetalol was 0.45–1.0 mg kg^{-1} (mean = 0.69 (0.10) mg kg^{-1}). There was no reduction in HR after labetalol. Induction of anaesthesia caused no significant change in either HR or arterial pressures. In the placebo group, tracheal intubation caused a 33% increase in HR above baseline ($P < 0.001$) and a 52% increase in MAP ($P < 0.001$); these changes were greater than the corresponding changes observed in the labetalol group (7.3% and 21.3%, respectively; $P < 0.05$ for MAP only). Two patients in the control group developed more than five premature ventricular contractions associated with tracheal intubation, compared with none in the labetalol-treated group. The average duration of laryngoscopy was 16 (3) s in the placebo group and 18 (2) s in labetalol treated patients. MAP decreased in two patients to 50–60 mm Hg at 40 and 65 min after surgical incision, respectively, in patients who received labetalol 0.75 or 1 mg kg^{-1}. End-

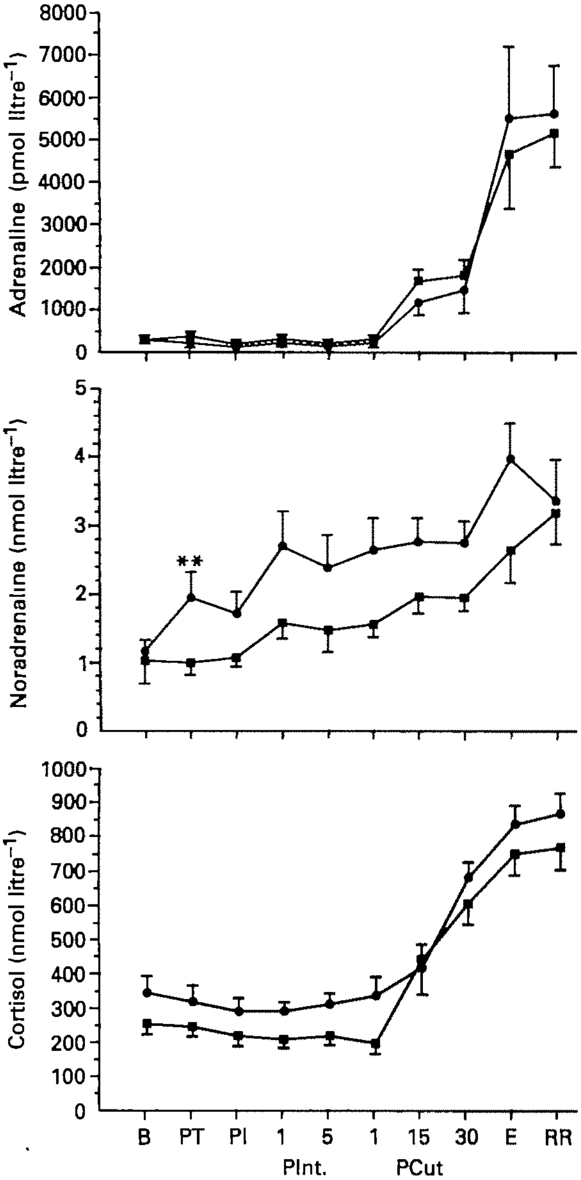

FIG. 2. Mean values for plasma concentrations of adrenaline, noradrenaline and cortisol. (For explanation of time points, see legend to figure 1.) Intergroup differences: $^{**}P < 0.01$.

expiratory isoflurane concentrations at those times were 0.8% and 0.95%, respectively. No patient required vasopressor therapy during the study. At the time of tracheal extubation, the patients treated with labetalol had a significantly slower HR ($P < 0.05$), whereas SAP, MAP and DAP were similar to values in the placebo-treated control group.

Hormonal responses

The plasma concentrations of adrenaline and noradrenaline for both groups are shown in figure 2. Before induction, labetalol caused a 62.3% increase in plasma concentration of noradrenaline compared with placebo ($P < 0.003$). Further increases during tracheal intubation and surgery were similar in both groups (figure 2). Neither induction of anaesthesia nor tracheal intubation caused significant changes in plasma concentration of adrenaline in both groups. Surgical stimulation caused a substantial increase in plasma concentration of adrenaline ($P < 0.001$) in both groups, to approximately 50-fold greater than baseline, which persisted into the early recovery period.

Plasma concentrations of cortisol and aldosterone (fig. 2, table II) exhibited similar patterns. Plasma renin activity was decreased (normal range 0.56–2.1 ng litre^{-1} s) throughout the study (table II). Plasma concentration of potassium was unchanged in both groups until the postoperative period. The control group had a lesser ($P < 0.05$) plasma concentration of potassium in the recovery room (3.4 (0.1) mmol litre^{-1} *vs* 3.8 (0.1) mmol litre^{-1}). Arterial $P\text{o}_2$ values were similar in both groups. Plasma concentrations of labetalol (fig. 3) were compatible with the known rapid distribution of labetalol into the proposed two-compartment model [22].

DISCUSSION

Previous clinical trials investigating the use of labetalol showed variable success in attenuating heart rate and arterial pressure responses to tracheal intubation [10–15]. In our study, observations over the entire operative course suggest an initial α-adrenoceptor effect manifest by a decrease in MAP followed by a sustained β-adrenergic blocking effect on heart rate during tracheal extubation and early recovery. Two patients receiving labetalol $\geqslant 0.75$ mg kg^{-1} developed a transient decrease in MAP during surgery. Thus it would seem prudent not to administer doses of labetalol > 0.5 mg kg^{-1} before induction of anaesthesia.

We observed a small but significant increase in plasma concentrations of noradrenaline in response to intubation in both groups. This and other [2, 23–25] studies suggest that noradrenaline is the primary neurotransmitter responsible for

TABLE II. *Mean* (SEM) *plasma concentrations of renin and aldosterone*

	Plasma renin activity (ng litre^{-1} s)		Plasma aldosterone concn (pmol litre^{-1})	
	Placebo	Labetalol	Placebo	Labetalol
Baseline	0.31 (0.06)	0.33 (0.09)	1415 (333)	888 (200)
Post-incision				
1 min	0.25 (0.06)	0.41 (0.17)	1207 (269)	816 (247)
30 min	0.47 (0.11)	0.50 (0.22)	3956 (1101)	1800 (585)
Recovery room	0.41 (0.11)	0.36 (0.11)	9043 (2721)	5348 (1612)

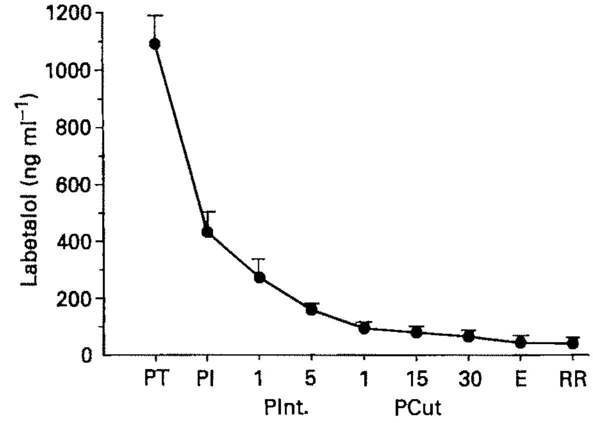

FIG. 3. Mean (SD) plasma concentrations of labetalol after titration of labetalol and throughout the study. (For explanation of time points, see legend to figure 1.)

the haemodynamic changes, and combined α- and β-adrenergic block is a logical treatment.

The dissociation seen in the control group between the increased plasma catecholamine concentrations in early recovery and the absence of tachycardia and hypertension, has been described previously [2], and may represent the occurrence of down-regulation of the β-adrenergic receptors [23, 26]. Although the use of small doses of fentanyl and droperidol at the time of peritoneal closure may have affected plasma concentrations of catecholamines, it would seem unlikely given the appreciable hormonal response seen during that time.

Plasma concentration of potassium was significantly less in the placebo group in early recovery, presumably because of β-adrenergic activity [27]. Rapid decreases may occur in the perioperative period [28] and may precipitate arrhythmias [29]. No patient receiving labetalol developed an arrhythmia during tracheal intubation, compared with two patients in the control group. This may be a result of a protective effect of labetalol on the myocardium or its Class I antiarrhythmic effect [30].

In conclusion, labetalol, in a dose sufficient to reduce MAP by 15%, abolished the HR response to tracheal intubation and significantly attenuated the pressor response. Greater doses of labetalol may cause significant hypotension.

ACKNOWLEDGEMENTS

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EFFECT OF SINGLE DOSES OF CISAPRIDE AND RANITIDINE ADMINISTERED SIMULTANEOUSLY ON PLASMA CONCENTRATIONS OF CISAPRIDE AND RANITIDINE

D. J. ROWBOTHAM, K. MILLIGAN AND P. McHUGH

SUMMARY

We have studied in 12 volunteers the effect of single doses of cisapride and ranitidine, administered simultaneously, on plasma concentrations of cisapride and ranitidine. Median maximum plasma concentration of ranitidine was achieved 1 h earlier when ranitidine was taken with cisapride compared with ranitidine alone ($P = 0.012$*). There was a 24% decrease in plasma ranitidine* $AUC_{8\,h}$ *when ranitidine was taken with cisapride compared with ranitidine alone (*$P < 0.005$*). Ranitidine had no effect on absorption of cisapride.*

KEY WORDS

Gastrointestinal tract: cisapride, gastric emptying, ranitidine. Pharmacokinetics: cisapride, ranitidine, interactions.

Cisapride is a new gastrointestinal prokinetic agent which increases gastric emptying in a variety of patients with gastroparesis [1–3] and increases lower oesophageal sphincter pressure [4]. When given i.m., cisapride is more effective than metoclopramide in preventing morphine-induced delay in gastric emptying [5].

Histamine H_2-receptor antagonists and metoclopramide are given frequently before anaesthesia if there is concern regarding inhalation of stomach contents, especially in obstetric practice. If cisapride was to be used also for this indication, it is likely that it would be taken concomitantly with histamine H_2-receptor blockers on many occasions.

Kirch and colleagues [6] showed that oral cisapride, when taken concomitantly with cimetidine, reduced time to maximum plasma concentration (tC_Pmax) and area under the concentration–time curve (AUC) of cimetidine significantly. Furthermore, cimetidine increased maximum plasma concentration ($C_P$max) and AUC of cisapride significantly.

Ranitidine is another histamine H_2-receptor antagonist used extensively in anaesthetic practice. Relatively fewer pharmacokinetic interactions have been reported compared with those for cimetidine [7]. It was the purpose of this study to investigate the effect of concomitant administration of cisapride and ranitidine on plasma concentrations of cisapride and ranitidine in volunteers.

SUBJECTS AND METHODS

After local Ethics Committee approval and written informed volunteer consent were obtained, we studied 12 healthy, non-smoking male subjects aged 18–55 (mean 25.4) yr, within 15% of normal height:weight ratio (mean weight 76.6 (SD 7.0) kg). Subjects were excluded if they were taking any medication or had clinical evidence of any medical disorder or drug abuse.

All subjects received three treatments in a randomized, three-way cross-over design, with treatments given at least 1 week apart. Subjects were investigated in the morning, having received nil-by-mouth since midnight.

The treatments were ranitidine 150 mg (1 tablet) plus cisapride 10 mg (1 tablet); ranitidine

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150 mg (1 tablet); cisapride 10 mg (1 tablet). Each treatment was taken with water 100 ml and tablets were swallowed without being chewed, with the subject in the sitting position.

Blood 10 ml was taken from an indwelling venous cannula before the study, and at 0.5, 1, 1.5, 2, 3, 4, 6 and 8 h after the treatment. Subjects remained seated during the first 2 h of the study. Plasma was separated immediately and stored at −20 °C.

Plasma concentrations of cisapride were measured by high performance liquid chromatography (HPLC) [8]. The lower limit of detection was 1 ng ml^{-1} and the mean coefficient of variation was 4.8%. Plasma concentrations of ranitidine also were measured by HPLC [9]. The lower limit of detection was 2 ng ml^{-1} and the mean coefficient of variation was 2%. Neither drug interfered with measurement of the other using these techniques.

AUC was calculated using the trapezoid method [10]. Cisapride and ranitidine AUC and $C_p$max were compared using paired Student's t test and tC_pmax with the Wilcoxon matched pairs signed rank test.

RESULTS

All subjects completed the study and there were no adverse effects.

Mean (SEM) plasma concentrations of cisapride are shown in figure 1. Mean (SEM) cisapride $C_p$max and AUC$_{8\text{ h}}$, and median tC_pmax values in each group are shown in table I. There were no significant differences between treatments.

Mean (SEM) plasma concentrations of ranitidine are shown in figure 2. Mean (SEM) ranitidine $C_p$max and AUC$_{8\text{ h}}$ and median (range) tC_pmax in each group are shown in table II. Median ranitidine tC_pmax was achieved 1 h earlier when

TABLE I. *Mean (SEM) cisapride $C_p$max and AUC$_{8\text{ h}}$, and median (range) tC_pmax. No significant differences*

Treatment	$C_p$max (ng ml^{-1})	tC_pmax (h)	AUC$_{8\text{ h}}$ (ng ml^{-1} h)
Cisapride	36.3 (3.3)	1.5 (1–6)	183 (16)
Cisapride + ranitidine	36.6 (3.7)	1.75 (1–6)	193 (18)

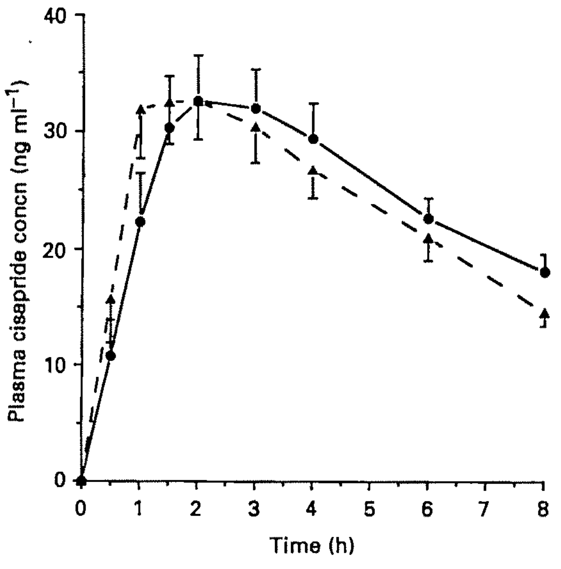

FIG. 1. Mean (SEM) plasma concentrations of cisapride in groups of volunteers receiving cisapride only (▲) or cisapride plus ranitidine (●).

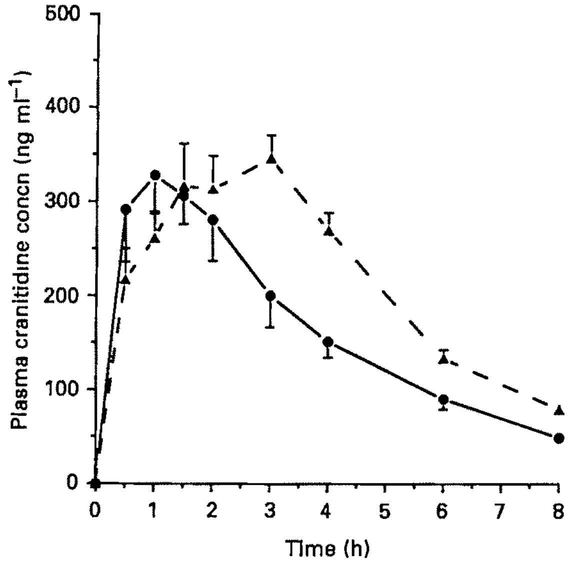

FIG. 2. Mean (SEM) plasma concentrations of ranitidine in groups of volunteers receiving ranitidine only (▲) or ranitidine plus cisapride (●).

TABLE II. *Mean (SEM) plasma ranitidine $C_p$max and AUC$_{8\text{ h}}$, and median (range) tC_pmax. **$P < 0.01$; ††$P = 0.012$ between groups*

Treatment	$C_p$max (ng ml^{-1})	tC_pmax (h)	AUC$_{8\text{ h}}$ (ng ml^{-1} h)
Ranitidine	437 (29)	1.75 (0.5–4)††	1724 (69)**
Cisapride + ranitidine	433 (40)	0.75 (0.5–2)	1310 (117)

ranitidine was taken with cisapride compared with ranitidine alone ($P = 0.012$). There was a 24% decrease in $AUC_{8\,h}$ when ranitidine was taken with cisapride compared with ranitidine alone ($P < 0.005$). There was no difference between the groups with respect to ranitidine $C_P$max.

DISCUSSION

Median ranitidine tC_Pmax was achieved 1 h earlier, but ranitidine $AUC_{8\,h}$ was reduced by 24% when ranitidine was taken with cisapride. Ranitidine had no effect on cisapride concentrations.

It is likely that the earlier ranitidine tC_Pmax resulted from an increased rate of ranitidine absorption associated with cisapride-induced increase in gastric emptying. Similar results have been shown with diazepam [11].

There are several explanations for the reduction of ranitidine $AUC_{8\,h}$ when taken with cisapride. The most likely explanation is that a cisapride-induced increase in gastrointestinal transit reduced ranitidine bioavailability by decreasing the time available for absorption from the gastrointestinal tract. Cisapride may have changed hepatic blood flow or clearance, but there are no data available to support this. Another explanation for these data is that cisapride reduced ranitidine half-life. This is unlikely, but cannot be excluded with certainty, as blood was not sampled for sufficient time in this study to allow reliable extrapolation of the plasma concentration–time curve in order to calculate half-life. An increase in volume of distribution of ranitidine also would reduce AUC, but this is unlikely as ranitidine $C_P$max was unaffected by cisapride. It is likely, therefore, that bioavailability of ranitidine at 8 h when taken with cisapride was reduced because of a cisapride-induced increase in gastrointestinal transit interfering with ranitidine absorption. It is not possible to comment on total bioavailability from these data, as insufficient blood samples were taken.

The interaction of cisapride and ranitidine is of potential importance. Ranitidine and cisapride are likely to be prescribed concomitantly in gastroenterological practice for the treatment of reflux oesophagitis [12]. Furthermore, if oral cisapride is to be used in anaesthetic practice, it is likely to be given to patients receiving ranitidine also, especially to patients in labour. This study has shown that cisapride is likely to have a beneficial effect on the time of onset of ranitidine-induced histamine H_2-receptor block, although further work is needed to confirm this.

The reduction in bioavailability is not likely to be of clinical importance if ranitidine is administered regularly. However, it is conceivable that the duration of action of a single dose of oral ranitidine may be shortened if taken with cisapride.

The interaction between cisapride and cimetidine on steady-state pharmacokinetics of both drugs was investigated by Kirch and colleagues [6]. After concomitant administration of cimetidine 400 mg three times a day and cisapride 10 mg three times a day for 1 week, cisapride shortened mean cimetidine tC_Pmax from 1.3 to 0.6 h ($P < 0.005$), but reduced bioavailability of cimetidine significantly. These findings are similar to those with ranitidine in the present study. However, cimetidine increased cisapride $C_P$max and cisapride $AUC_{0-24\,h}$ significantly, suggesting that cimetidine inhibits cisapride metabolism. We are not aware of any published data on steady-state pharmacokinetics of cisapride and ranitidine.

The effect of cisapride on the absorption of other drugs has been described. Cisapride 10 mg orally and 8 mg i.v. increased the absorption rate of diazepam, but with no change in total bioavailability [11]. In contrast, cisapride 10 mg three times a day taken with digoxin 0.25 mg twice daily by six healthy volunteers for 7 days had no significant effect on digoxin $C_P$max and bioavailability; however, the numbers in this study were small and the results only just failed to reach significance [13].

This study suggests that ranitidine absorption rate is increased when taken concomitantly with cisapride. This may be a beneficial interaction when these drugs are administered together to patients before surgery.

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EFFECTS OF EXTRADURAL ANAESTHESIA ON UMBILICAL AND UTEROPLACENTAL ARTERIAL FLOW VELOCITY WAVEFORMS

G. A. TURNER, J. P. NEWNHAM, C. JOHNSON AND M. WESTMORE

SUMMARY

Flow velocity waveforms were recorded from the umbilical artery and uteroplacental arterial circulations of 15 women undergoing elective Caesarean section under extradural anaesthesia. The systolic:diastolic ratios of the flow velocity waveform were determined before and after extradural block. Extradural block did not alter fetal or maternal heart rates; however, umbilical artery systolic:diastolic ratio decreased from a mean (SD) of 2.4 (0.42) to 2.26 (0.38) (P = 0.049). There were no significant changes in the uteroplacental systolic:diastolic ratios. These results were compared with those from a control group in which no statistically significant changes in maternal and fetal systolic:diastolic ratios or heart rates were observed. The application of a pulse correction factor to standardize the data to fixed maternal and fetal heart rates had little effect on the significance of the findings. Extradural block in normal pregnant women during late gestation was associated with a small reduction in umbilical artery systolic:diastolic ratios, suggesting a decrease in downstream fetoplacental vascular resistance.

KEY WORDS

Anaesthetic techniques extradural. Arteries. umbilical blood flow. Placenta: blood flow.

Extradural anaesthesia has become a widely used technique for Caesarean section. It allows the woman to remain awake, enabling immediate contact with her infant and minimizing her risk of pulmonary aspiration. The fetus also may benefit from reduced exposure to anaesthetic drugs [1].

Recent advances in ultrasonography have allowed study of the uteroplacental and fetoplacental circulations. Several preliminary investigations of the effects of extradural anaesthesia on the uteroplacental and fetoplacental circulations have been published, reporting conflicting results [2–6]. The technique used most frequently utilizes continuous wave Doppler ultrasound to obtain a flow velocity waveform of the blood flow through an umbilical or uteroplacental artery. By determining the ratio of peak flow in systole to least flow in diastole, an assessment of the downstream vascular resistance is obtained. Increased systolic:diastolic ratios have been correlated with increased placental vascular resistance caused by a decrease in the small arteries in placental tertiary stem villi [7] and have been reproduced in experimental animals by microsphere embolization of the umbilical circulation [8]. The purpose of this study was to use flow velocity waveform analysis to investigate the effects of extradural block on uteroplacental and fetoplacental vascular bed resistance. As systolic:diastolic ratios have negative correlations with their corresponding heart rates, allowance was made for the effect of pulse interval by adjustment of ratios to standard heart rates [9]. A control group also was included, to assess any changes in systolic:diastolic ratios which may have resulted solely from enforced rest.

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PATIENTS AND METHODS

We studied 15 women undergoing elective Caesarean section between 38 and 41 weeks gestation. All were ASA grade I with no history of problems during their pregnancy; in particular, none had any features of pre-eclampsia, diabetes, antepartum haemorrhage, abnormal amniotic fluid volume, uterine abnormality or altered fetal growth.

Informed consent was obtained from the patients and approval from the hospital Ethics Committee. The flow velocity waveforms were obtained with a Doptek spectrum analyser 9000 with a 4-MHz continuous wave Doppler transducer using methodology outlined elsewhere [10]. Briefly, ultrasound imaging was used to establish the site of the umbilical cord and placenta. The arterial waveforms were obtained by directing the Doppler beam and searching for the characteristic waveform. Systolic:diastolic ratios were recorded from umbilical and uteroplacental arterial waveforms and calculated from the mean of three or four consecutive waveforms. Measurements were not made during periods of fetal breathing or excessive fetal activity and at least 10 stable consecutive waveforms were required before measurements were taken. Heart rates were calculated from measurement of the average pulse interval using electronic calipers. Results of the Doppler studies were not released for clinical management.

Readings were performed by the principal author (G.T.). An analysis of within-observer variability showed a coefficient of variability of less than 5% within a series of measurements in the same patient. All measurements were made with the woman in a left lateral tilt position to avoid aortocaval compression. Baseline readings were made before preloading with Hartmann's solution 1000 ml. An extradural catheter was inserted into the lumbar extradural space through a 16-gauge Tuohy needle and anaesthesia was induced with introducing 0.5% plain bupivacaine 15 ml. Further increments of 0.5% bupivacaine were added to obtain a sensory block to the level of T3–5. Arterial pressure measurements were made at 5-min intervals. A second set of readings and recording of the height of the block were made after another 20 min.

The control patients had two sets of readings made 40 min apart while lying on a theatre trolley in the left lateral position, in the same operating suite recovery room. The patients remained on the trolley between the readings and were exposed to the theatre suite environment. Neither an i.v. nor an extradural catheter was inserted. Thus any change in the fetoplacental or maternoplacental flow velocity waveforms caused solely by a period of enforced rest in the operating theatre environment could be assessed.

The potential exists for uteroplacental systolic: diastolic ratios to vary with the site along the uterine arterial tree that the measurement is taken. Measurement from arteries close to the placental bed may result in smaller systolic:diastolic ratios, reflecting the low resistance of the placental vasculature, while measurements taken from a more proximal site may result in greater systolic: diastolic ratios, reflecting the low resistance placental and high resistance somatic arteries downstream. Great care was taken in the present study to ensure that measurements were taken from arteries within the centre of the placental bed and in each patient serial measurements were taken from the same site.

The effects of extradural anaesthesia on heart rates and flow velocity waveform systolic:diastolic ratios were tested by paired Student's *t* tests. Logarithmic (base 10) transformations were performed if systolic:diastolic ratios were not normally distributed.

RESULTS

There were 15 patients in the extradural group and seven patients in the control group, matched for maternal and gestational age. Mean maternal ages were 29.2 yr and 29.3 yr, for the control and extradural groups, respectively; mean gestational ages were 38.8 weeks and 39.2 weeks, respectively. Mean maternal systolic arterial pressure before and after extradural block were 109.2 (SD 10.9) and 109.3 (9.3), respectively. No vasopressors were required by any of the patients during the period of the post-extradural observations.

The effects of extradural anaesthesia on umbilical artery systolic:diastolic ratios are shown in table I. Extradural anaesthesia was followed by a reduction in umbilical artery systolic:diastolic ratios from mean (SD) 2.40 (0.42) to 2.26 (0.38) ($P = 0.049$). Although there was a mean reduction in umbilical artery systolic:diastolic ratio, the effect of extradural anaesthesia was variable, with an increase in four patients, no change in five patients and a decrease in six. Umbilical artery systolic:diastolic ratios at corresponding times in the control group were not altered ($P = 0.16$).

TABLE I. *Umbilical and uterine artery systolic:diastolic ratios before (A) and after (B) extradural block and at times 0 min (A) and 40 min (B) in a control group of subjects.* *P<0.05 *compared with before block*

Subject No.	Umbilical artery systolic:diastolic ratio		Uterine artery systolic:diastolic ratio	
	A	B	A	B
Extradural group				
1	1.9	2.0	1.33	1.53
2	3.25	2.77	1.66	1.74
3	3.02	3.32	1.76	1.63
4	2.01	1.99	1.38	1.53
5	2.31	2.26	1.35	1.59
6	2.24	2.24	1.91	1.44
7	2.11	2.12	1.60	1.28
8	2.13	2.08	1.44	1.85
9	2.51	2.08	1.39	1.41
10	2.23	1.84	1.56	1.55
11	2.87	2.35	1.78	2.00
12	2.54	1.95	1.54	1.61
13	2.13	2.33	1.48	1.42
14	2.05	2.41	1.31	1.26
15	3.08	2.67	1.66	1.86
Mean	2.4	2.26*	1.54	1.56
SD	0.42	0.38	0.18	0.2
Control group				
1	2.0	2.6	1.65	1.55
2	2.37	2.26	1.42	1.41
3	2.16	2.88	1.75	1.39
4	2.3	2.48	1.3	1.35
5	2.39	2.33	1.7	1.59
6	2.34	2.33	1.42	1.45
7	2.73	2.48	1.37	1.30
Mean	2.33	2.48	1.52	1.43
SD	0.23	0.21	0.18	0.1

Fetal heart rates before and after extradural anaesthesia were similar. After adjustment of the ratios to a standard rate of 140 beat min^{-1}, mean (SD) ratios decreased from 2.32 (0.61) to 2.20 (0.61) ($P = 0.054$). The relative magnitude of this decrease was not significantly different from that observed when the systolic:diastolic ratios had not been adjusted for heart rate.

Maternal uteroplacental systolic:diastolic ratios are shown in table I. Extradural anaesthesia was not associated with an alteration in uteroplacental systolic:diastolic ratios or maternal heart rates. Adjustment of the systolic:diastolic ratios to a standard rate of 80 beat min^{-1} did not affect the significance of this response.

DISCUSSION

The use of Doppler ultrasound has permitted *in vivo* assessment of flow through the uteroplacental and fetoplacental vascular beds. Spectrum analysis of the Doppler shift provides an assessment of the velocity of the red blood cell mass moving through the vessel. With the continuous wave Doppler technique used in the present study, systolic:diastolic ratios from the flow velocity waveform are calculated to provide an assessment of downstream vascular resistance. Actual flow rates cannot be calculated, as the angle of insonation is unknown. The results of the present study indicate that, after extradural anaesthesia was established, there was a reduction in mean umbilical artery systolic:diastolic ratios which suggests a decrease in downstream fetoplacental vascular resistance. However, other factors also may have contributed to this decrease in umbilical artery systolic:diastolic ratios. Flow rates through a given vessel vary inversely, not only with the resistance of the downstream vascular bed, but also with the viscosity of the perfusing fluid. Nevertheless, Steel and colleagues [11] found that changes in viscosity contributed only 10% to the variability in flow velocity waveforms obtained from the uteroplacental circulation. Similarly, Giles and Trudinger [12] were unable to demonstrate that alterations in flow velocity waveforms were caused by changes in whole blood viscosity. Therefore it is difficult to attribute the decreased systolic:diastolic ratio in the fetoplacental circulation to haemodilution secondary to the preload of Hartmann's solution 1000 ml. Blood flow through vascular beds also varies with perfusion pressure, which may be measured and controlled to some extent on the maternal side, but must be assumed to remain relatively unchanged in the fetal circulation.

Previous studies of the effects of extradural block on systolic:diastolic ratios have produced conflicting results [2–6]. No changes were observed in umbilical systolic:diastolic ratio after extradural block both in studies in which adrenaline was added to the local anaesthetic solution [2, 4] and in studies in which it was omitted [5]. Our results are consistent with those of Giles, Lah and Trudinger [3] which demonstrated a reduction in systolic:diastolic ratio after establishment of a block. None of the previous studies took account of the potential influence of maternal and fetal heart rates. However, adjustment of systolic:diastolic ratios to standard heart rates had minimal effect on the trend or significance of our finding, probably because maternal and fetal heart rates were little changed after extradural block.

There is evidence that the fetoplacental and uteroplacental circulations are matched to optimize nutrient and waste exchange and thus changes in one may influence the other [13]. Therefore, to analyse changes in the fetoplacental flow velocity waveforms, simultaneous recording of changes in the uteroplacental flow velocity waveforms are of interest. Of the previously cited studies, only two have taken measurements from both circulations. Giles, Lah and Trudinger [3] found that the uteroplacental systolic:diastolic ratio decreased in parallel with the umbilical systolic:diastolic ratio, while Baumann and colleagues [6] found an increase in uteroplacental resistance indices, but no changes in fetoplacental resistance. Our study provides a third combination of no change in uteroplacental systolic:diastolic ratio with a decrease in mean umbilical systolic:diastolic ratio.

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PHARMACOKINETICS AND DISTRIBUTION OF KETAMINE AFTER EXTRADURAL ADMINISTRATION TO DOGS

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SUMMARY

We have studied the pharmacokinetics and distribution of ketamine and its biotransformation products in dogs after extradural administration of ketamine at L4–5. The mean apparent uptake rate constants of ketamine for plasma and CSF were 4.17 (SD 1.84) and 5.15 (2.50) h^{-1}, respectively. The concentrations of ketamine in CSF were greater than those found in plasma. The elimination half-life values of the parent drug for both biological fluids were similar (4.3 (2.96) h and 4.6 (3.31) h for plasma and CSF, respectively). The apparent formation rate constant of norketamine was greater than that of dehydronorketamine. However, the concentrations of the biotransformation products in CSF were smaller than those of the parent drug. These results are similar to the distribution of ketamine and its metabolites in different cerebral structures and tissues. The concentrations decreased in concert with the increase in polarity of the metabolites. A specific distribution for all compounds was observed. Ketamine showed a greater affinity for brainstem, while norketamine and dehydronorketamine were distributed mostly in cerebellum and kidney, respectively.

KEY WORDS

Anaesthetics, intravenous. ketamine Anaesthetic techniques extradural Pharmacokinetics ketamine.

In recent years the number of drugs administered by intrathecal and extradural routes has increased considerably [1]. The existence of opioid receptors in the spinal cord permits use of these routes as an alternative to parenteral administration of analgesics [2]. It has been suggested that ketamine may be administered via these routes [3]. There is evidence to suggest that ketamine binds stereospecifically to opioid receptors in the brain and spinal cord [4]. Although some pharmacodynamic studies have been carried out [3], only one has evaluated the pharmacokinetics of ketamine after extradural administration [5]; in that study only plasma concentrations were measured. Because ketamine probably has a site of action in the spinal cord and brain, and as one of its metabolites probably contributes to the pharmacological effects observed, more information may be obtained by studying the kinetics of ketamine and its biotransformation products in plasma, cerebrospinal fluid (CSF) and its redistribution in the brain.

The purpose of the present study was to examine the disposition of ketamine and its biotransformation products in plasma, CSF, different brain structures and other tissues after extradural administration.

MATERIALS AND METHODS

Animals

Four mongrel dogs of both sexes were studied (mean weight 20.7 (SD 0.9) kg). All were fasted with water *ad libitum* for 12 h before each study.

This study fulfilled the requirements for the protection of experimental animals established by Spanish legislation and EC rules.

Induction and maintenance of anaesthesia

The animals were anaesthetized with thiopentone 20–30 mg kg^{-1} i.v. The trachea was intubated

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and mechanical ventilation initiated at a tidal volume of 300 ml and ventilatory frequency of 30 b.p.m., adjusted to maintain normal arterial blood-gas tensions.

Anaesthesia was maintained with 1 % isoflurane in oxygen. Neuromuscular blocking drugs were avoided. Rectal temperature was monitored and maintained at 38 ± 1 °C with a thermal blanket.

Catheterization

After anaesthesia, a polyethylene catheter was placed in the right carotid artery for obtaining blood samples for measurement of blood-gas tensions and for monitoring arterial pressure. A femoral vein was cannulated to permit administration of fluids and a femoral artery was cannulated for obtaining blood samples. Urine samples were collected after catheterization of the bladder. CSF samples were obtained via a 60-cm polyethylene catheter (PE50, 0.6 mm i.d., 0.1 mm o.d.) placed at the C1–2 vertebral level.

Administration and sampling

Ketamine was administered at a dose of 3 mg kg^{-1} (similar to the dose in humans) in isotonic saline 2 ml by lumbar puncture at L4–5 using a fine needle (o.d. 0.5 mm). CSF samples (0.2 ml) and blood 1 ml were collected simultaneously before and 5, 10, 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, 8 and 9 h after administration of ketamine. The blood was collected into heparinized tubes and centrifuged at 3000 *g* for 15 min. After each sampling, the CSF that had been removed was replaced by an equivalent volume of artificial CSF. At the same times, the volume of urine was measured and one aliquot was collected. At 9 h after administration of the drug, the animals were killed by a large dose of thiopentone; tissues were removed (mesencephalon, cerebellum, brain, brainstem, protuberance, spinal cord, heart, kidney, liver, lung, muscle and skin) to assay concentrations of ketamine and its biotransformation products. The samples of plasma, CSF, urine and tissues were stored at −20 °C until required for assay.

Analytical technique

Measurement of ketamine and its biotransformation products in plasma, CSF, urine and tissues was performed by gas chromatography with an electron capture detector as reported elsewhere [6]. The tissues were homogenized in saline solution at a proportion of 1:5 (wet weight: volume). The mean tissue recovery for the three substances was greater than 80 %. The technique is based on double extraction and derivatization with heptafluorobutyric anhydride. Briefly, 1 ml of biological sample, alkalinized with sodium hydroxide 1 mol $litre^{-1}$, was extracted with chloroform 5 ml. After 15 min of centrifugation, the chloroform layer was transferred to glass tubes containing 3 ml of hydrochloric acid 0.1 mol $litre^{-1}$. After 15 min of centrifugation, the hydrochloric phase was transferred to other glass tubes containing hexane 5 ml and 0.5 ml of sodium hydroxide 10 mol $litre^{-1}$. These tubes were centrifuged and the last organic phase utilized for derivatization of ketamine and its metabolites for assay. This procedure consisted of the addition of pyridine 50 µl and heptafluorobutyric anhydride 50 µl, and heating for 30 min in a water bath (40 °C) and the excess of heptafluorobutyric anhydride was neutralized by addition of 5 ml of sodium hydroxide 0.5 mol $litre^{-1}$. The tubes were shaken and centrifuged to separate the organic phase, which was transferred to other tubes containing 5 ml of hydrochloric acid 0.25 mol $litre^{-1}$. After shaking and centrifugation, the organic phase was evaporated to dryness under a stream of nitrogen, the residue was redissolved in hexane 100 µl and 1 µl was injected onto the chromatograph. The instruments used were a Varian mod 3700 gas chromatograph equipped with an electronic capture detector and a Varian mod CDS 111 digital integrator. The 2 m × 2 mm (i.d.) column was packed with 3 % OV-17 on Gas Chrom-Q 100/120 mesh. The detector and injector temperatures were 250 °C and 210 °C, respectively. The column was heated to 195 °C, with a gas carrier (nitrogen) flow of 40 ml min^{-1}. The variation coefficients of the technique were 5.45, 5.49 and 4.15 % for ketamine, norketamine and dehydronorketamine, respectively. The sensitivity limits of the same substances were 50, 5 and 50 ng ml^{-1}. No differences between these coefficients were present for the different biological samples studied.

Pharmacokinetic analysis

Compartmental analysis. The time course of plasma and CSF concentrations of ketamine were fitted to the following triexponential equations:

$$\text{Plasma}: C = Ae^{-k_1 t} + Be^{-k_2 t} + Ce^{-k_3 t}$$

$$\text{CSF}: C = A'e^{-k'_1 t} + B'e^{-k'_2 t} + C'e^{-k'_3 t}$$

where k_1, k_2 and k_3 = apparent rate constants of absorption, distribution and elimination of the parent drug in plasma; k'_1, k'_2 and k'_3 = apparent rate constants of uptake of the drug into CSF and its distribution and elimination from this fluid, respectively.

The time course of the metabolites of ketamine in plasma and CSF were fitted to the following biexponential equation:

$$C = A''e^{-k''_1 t} + B''e^{-k''_2 t}$$

where k''_1 = apparent rate constant of formation or incorporation of the metabolites into CSF; k''_2 = apparent rate constant of elimination of the biotransformation products from CSF or plasma.

The unweighted plasma and CSF concentrations were analysed by an iterative polyexponential curve stripping program (JANA) [7] on an IBM microcomputer. Best fits were obtained using a three-compartmental open model system for plasma and CSF concentrations of ketamine and a two-compartmental open model system for plasma and CSF concentrations of metabolites. The adequacy of the kinetic models was confirmed by examining the plots of residuals and the precision of the parameters estimates according to Boxenbaum, Riegelman and Elashoff [8].

The elimination half-lives of the drug and its metabolites from plasma and CSF were calculated using the following equation:

$$T_{\frac{1}{2}} = 0.693/k$$

where k = apparent elimination rate constant of ketamine, norketamine and dehydronorketamine from plasma and CSF.

Non-compartmental analysis. The maximum plasma and CSF concentrations (*C*max) and the times taken to reach these concentrations (*tC*max) were obtained from the experimental curves of ketamine and its biotransformation products in both fluids. The areas under the curve (AUC) were calculated from the area under the curve from time zero up to 9 h (obtained by the linear trapezoidal method) plus $C^{9\,h}/k$, where $C^{9\,h}$ = plasma or CSF concentration of ketamine, norketamine and dehydronorketamine at 9 h after administration and k = elimination constant of each of the compounds calculated from the slope of the end part of the plasma and CSF concentration curves [9].

Statistical analysis

In order to compare the values of the different pharmacokinetic parameters, one-way ANOVA test was performed [10].

RESULTS

The principal pharmacokinetic parameters of ketamine and its biotransformation products are summarized in table I.

Ketamine passed from the administration site to plasma and CSF rapidly, with mean apparent uptake rate constants of 4.17 (SD 1.84) h^{-1} and 5.15 (2.50) h^{-1}, respectively (fig. 1A). Ketamine concentrations in CSF were greater than those found in plasma throughout almost the whole of the experimental period. This is reflected also in the maximum concentrations of ketamine in CSF (4.92 (1.84) $\mu g\ ml^{-1}$), which were almost twice

TABLE I. *Pharmacokinetic parameters (mean* (SD) *[range]) of ketamine and its biotransformation products obtained after extradural administration of ketamine to dogs (L4–5 level).* †*Apparent rate constant of incorporation or formation of ketamine and its metabolites.* ‡*Calculated according to compartmental analysis.* §*Calculated according to non-compartmental analysis.* **Statistically significant difference* (P < *0.05) compared with same parameter in CSF*

	Ketamine		Norketamine		Dehydronorketamine	
	Plasma	CSF	Plasma	CSF	Plasma	CSF
k_1 (mg litre^{-1} h^{-1})†‡	4.17 (1.84) [1.66–5.67]	5.15 (2.50) [2.31–7.38]	2.98 (1.26) [1.22–3.93]	6.20 (4.03) [3.43–12.22]	0.91 (0.61) [0.51–1.80]	2.27 (2.87) [0.29–5.56]
$T_{\frac{1}{2}}$ (h)‡	4.29 (2.96) [1.92–8.60]	4.57 (3.31) [1.28–8.66]	2.44 (1.39) [1.23–4.07]	2.54 (2.54) [1.21–4.60]	3.09 (1.63) [1.58–5.33]	3.16 (1.55) [1.31–5.82]
*C*max (μg ml^{-1})§	2.46 (0.78) [1.36–3.19]	4.92 (1.84) [2.25–6.46]	0.30 (0.30) [0.10–0.74]	0.21 (0.10) [0.06–0.26]	0.22 (0.11) [0.09–0.36]	0.28 (0.10) [0.19–0.38]
*tC*max (h)§	0.44 (0.24) [0.25–0.75]	0.31 (0.13) [0.25–0.50]	0.94 (0.72) [0.50–2.00]	0.75 (0.20) [0.50–1.00]	1.94 (1.42) [0.75–4.00]	1.67 (0.58) [1.00–2.00]
AUC (μg h^{-1} ml^{-1})§	2.69 (1.44) [1.36–4.67]	6.95 (3.00) [3.48–9.83]	1.05 (1.01) [0.50–2.74]	0.66 (0.44) [0.15–1.20]	1.55 (1.08) [0.32–2.83]	0.98 (0.76) [0.48–1.85]

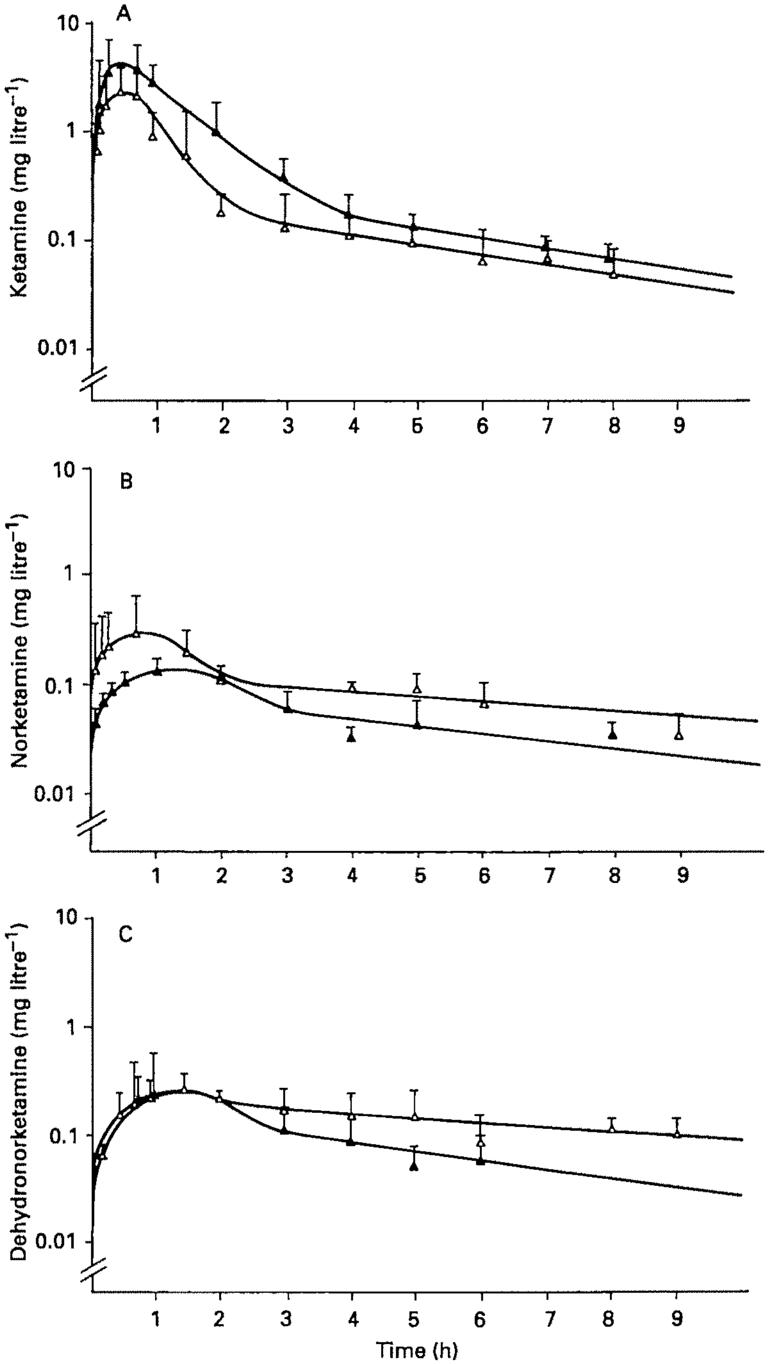

FIG. 1. Mean plasma (△) and CSF (▲) concentrations of ketamine (A), norketamine (B) and dehydronorketamine (C) after extradural administration of ketamine 3 mg kg^{-1} at the L4–5 level. (Missing data points are because of sample loss.)

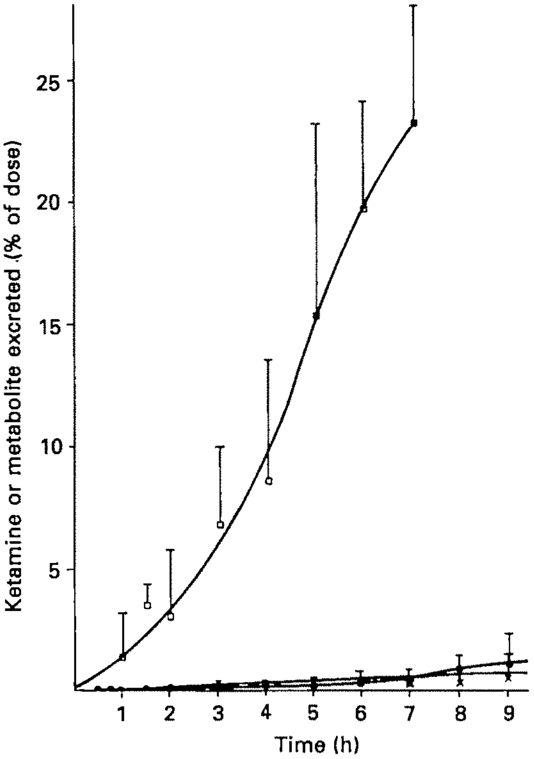

FIG. 2. Mean cumulative urinary excretion curves of ketamine (●), norketamine (×) and dehydronorketamine (□), after extradural administration of ketamine 3 mg kg^{-1} to dogs.

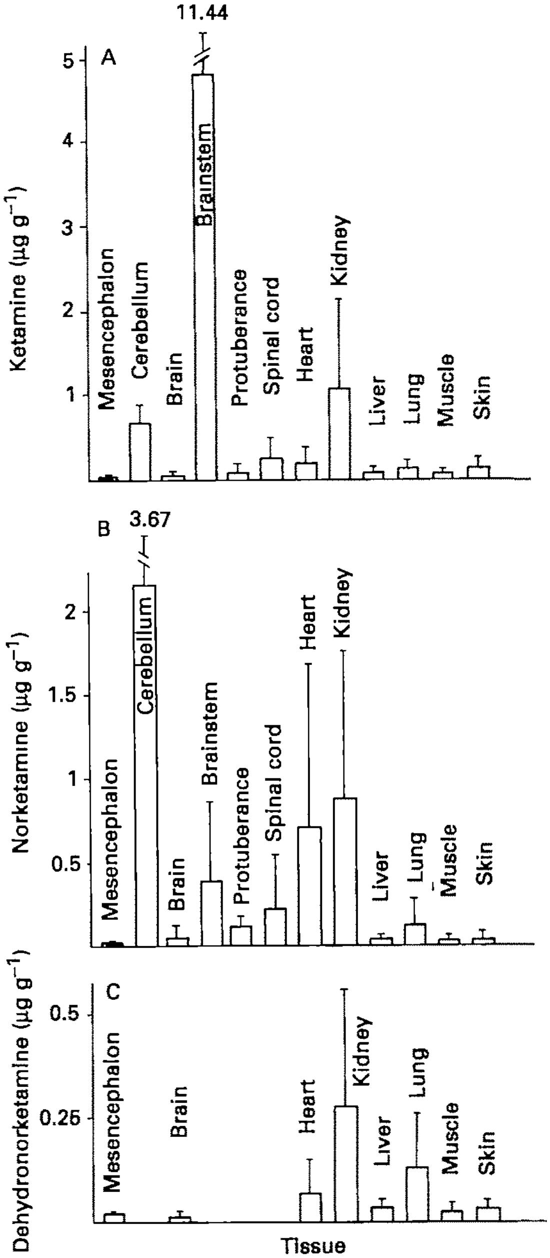

FIG. 3. Tissues concentrations of ketamine (A), norketamine (B) and dehydronorketamine (C) after extradural administration of ketamine 3 mg kg^{-1} to dogs. (Units are µg per gram of wet tissue.)

those in plasma (2.46 (0.78) µg ml^{-1}). Despite the differences in the maximum concentrations reached in both fluids, there were no statistically significant differences ($P > 0.05$) between the times at which the maximum concentration values were reached (0.31 (0.13) h *vs* 0.44 (0.24) h for CSF and plasma, respectively). This accounts for the greater value obtained in the AUC of ketamine concentrations for CSF compared with plasma.

The apparent formation rate constant of norketamine was greater than that of dehydronorketamine. (This metabolite represents an analytical artefact [11, 12] and it is representative of concentrations of hydroxylate metabolites.) Similar results have been reported in other species and for other routes of administration by different authors. This explains why the time taken by the demethylated derivative to reach its maximum plasma concentrations (0.94 (0.72) h) (fig. 1B) was less than that found for dehydronorketamine (1.94 (1.42) h) (fig. 1C). Nevertheless, no statistically significant differences ($P > 0.05$) were found between the values of the maximum plasma concentrations of the two metabolites.

Ketamine concentrations in plasma and CSF followed a biexponential decrease, unlike the time course of the biotransformation products, which was monoexponential. The elimination half-life values of the parent drug and its biotransformation products in both biological fluids were similar.

The cumulative urinary excretion curves of ketamine and its metabolites reveal that the total percentage eliminated at 9 h after administration was 26% of the dose administered (fig. 2). Of the total amount excreted at 9 h, 1.18% comprised unaltered drug, 0.74% was the demethylated derivative and 23.86% was dehydronorketamine.

Figure 3 illustrates the tissue concentrations of ketamine, norketamine and dehydronorketamine (expressed as µg/g of wet tissue).

DISCUSSION

The pharmacokinetics of the extradural route of drug administration are complicated because of different processes such as dural penetration, fat deposition, and systemic absorption. Other important factors include the physicochemical characteristics of the drug, such as its pK_a and degree of lipid solubility [13]. Ketamine is a very lipid soluble drug which is highly ionized at physiological pH. According to the physiological model proposed by Cousins and Mather [14], drugs of this type exhibit low concentrations of their non-ionized lipid soluble forms within the extradural space which are transferred rapidly to the CSF, nerve root arteries of the spine and extradural veins. Such processes account for the rapid increase in drug concentrations in CSF and plasma, as may be seen in figure 1A. Because of this, maximum concentrations of ketamine in plasma and CSF (2.46 and 4.92 µg ml^{-1}) were reached in a fairly short time (0.44 and 0.31 h, respectively). However, significant vascular absorption reduced the concentration gradient relatively quickly. Moreover, the pronounced lipid solubility of ketamine causes slow release of the drug from the lipid components of the spinal cord. These two aspects account for the change in the rate of access of ketamine with time to CSF and plasma and sustained concentrations in both fluids. These biphasic characteristics were observed also by Burm and colleagues [15] and Debruyne and colleagues [16] for some local anaesthetics after extradural and intraperitoneal administration, respectively. These authors demonstrated that the extent of biphasic change is a function of the physicochemical properties of the drug. The plasma half-life of ketamine after extradural administration was significantly greater than that obtained by Kaka and colleagues [17] after i.v. administration. This shows that the slow release of the drug from the site of administration is the process governing the time course of the concentrations of the drug on the terminal part of the CSF and plasma concentration curves. Similar results have been reported after extradural and i.v. administration to humans [5]. The slower absorption of ketamine, consistent with its physicochemical properties, suggests that systemic absorption plays a major role in the termination of the pharmacological effect and this may explain the prolonged maintenance of analgesic effects after ketamine administration via the extradural route.

As a result of the high vascular uptake and transfer of ketamine to CSF, there are no large differences between the concentrations reached in each biological fluid compared with other substances. The ratio between the two concentrations did not exceed 2, unlike other compounds such as morphine, with a low vascular re-uptake and a strong degree of migration towards CSF [18, 19]. For morphine, the ratio is approximately 100, and this explains the appearance of analgesic effects even when blood concentrations are small. In contrast, for ketamine there seems to be a correlation between the concentration of drug in plasma and the duration and intensity of pharmacological effects.

The time course of the plasma and CSF concentrations of norketamine and dehydronorketamine (figs 1B, 1C, respectively) reveal no statistically significant differences between their pharmacokinetic parameters, probably as a result of the small number of dogs studied and the considerable variability in time course of the plasma concentrations. However, it may be seen that the mean values of the constants characterizing the ascending part of the curve are greater for CSF than for plasma. Likewise, the time at which the maximum concentrations were reached in both fluids was shorter in CSF than in plasma. It may be assumed that biotransformation occurs only in the plasma compartment and that the metabolites are more water soluble than the parent drug; thus transfer to the CNS would be more limited and one would expect to observe smaller access rate constants and greater maximum time values for CSF than for plasma. The findings observed in the present study suggest that the CNS would contribute towards the increased concentrations of metabolites in the CSF. The capacity of cytochrome P450-dependent biotransformation in brain microsomes is well documented [20]. However, Cohen and colleagues [21], in *in vitro* biotransformation studies, have shown that brain tissue is not able to metabolize ketamine. Thus our conclusions are based only on indirect measurements and further studies are required for confirmation.

The cumulative urinary excretion values shown in figure 2 confirm the high degree of biotransformation of this drug. The major urinary excretion product was dehydronorketamine, which comprised 23.86 % of the total dose administered. Norketamine appeared in urine in small concentrations (0.74 %), as did the unaltered form of the drug (1.18 %). Such findings are similar to those obtained after other routes of administration.

The results of the distribution studies (fig. 3) show that there was a specific distribution of ketamine and its biotransformation products in the different tissues and brain structures studied. Whereas ketamine was located in greatest concentrations in the brainstem (mean value 4.78 μg g^{-1}), norketamine showed greater affinity for the cerebellum (mean value 2.15 μg g^{-1}). Cumulation of drug and metabolites in cerebral tissue is considered to be a function of blood flow and tissue solubility at physiological pH. A decrease in tissue concentrations occurs as the drug is biotransformed. This uneven distribution in brain has been observed also in rats for other drugs such as amitriptyline, nortriptyline, imipramine and chlorimipramine, and has been attributed to the existence of specific binding sites of the drugs in these structures [22].

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POSTOPERATIVE MYOCARDIAL ISCHAEMIA IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION

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SUMMARY

Fifteen patients (10 men and five women; mean age 67.3 yr) with a history of a recent (< 1 yr) myocardial infarction underwent ambulatory ECG monitoring for 5 days after non-cardiac surgery. The duration, number and severity of ischaemic episodes were maximal within the first 12 h after surgery and again on the 3rd day after operation. The difference in the duration of ischaemic episodes between the 2nd and 3rd days after operation was statistically significant (P < 0.05). There were no perioperative myocardial infarctions and all patients were discharged from hospital.

KEY WORDS

Heart: myocardial infarction, postoperative ischaemia. Monitoring: ambulatory ECG. Surgery: non-cardiac.

The prognosis of patients after myocardial infarction (MI) is related to evidence of active ischaemia, the extent of coronary artery disease and the residual left ventricular function [1]. Recent studies showed that objective myocardial ischaemia (silent or symptomatic) after MI increases the cardiac risk for anaesthesia [1]. In the perioperative period, myocardial ischaemia leading to infarction can occur throughout the perioperative period; the incidence peaks on the day of surgery and again on the 3rd day after operation [2, 3]. The ischaemic episodes may be silent in up to 61 % of patients [2, 3]. The aim of the current study was to investigate the degree of ischaemic changes in the ECG of patients with recent MI undergoing non-cardiac surgery.

METHODS AND RESULTS

Between September 1988 and September 1990, we studied all patients with a history of a recent myocardial infarction (< 1 yr) undergoing a non-cardiac surgical procedure. Approval by the Ethics Committee of the University and informed consent were obtained. A two-channel ambulatory ECG recorder (Tracker, Reynolds, Hertfort, England) was applied with the exploring leads in the CM_5 and CC_5 positions. Recording commenced immediately after surgery when the patient was transferred to the ICU and ended at the beginning of the 5th day after operation. The tapes were analysed at the end of the 5-day period by two independent cardiologists, who were not aware of the individual clinical course of the patient. A scanner unit was used for automatic and operator-controlled analysis.

The mean, maximal and minimal heart rate in each 24-h period and number, duration and severity of ST-segment changes in each 12-h period were recorded and evaluated. An ischaemic episode was defined as a transient ST-segment depression > 0.1 mV, 60 ms after the J-point and lasting for at least 1 min. ST-segment changes associated with bundle branch block, intraventricular conduction disturbances or pacemaker activity were excluded. T-wave abnormalities were not included in the analysis.

The Wilcoxon test for matched pairs (Bonferroni correction) was used to compare each pair of consecutive periods. $P < 0.05$ was considered statistically significant.

All patients received their usual medication, which was continued until the morning of surgery

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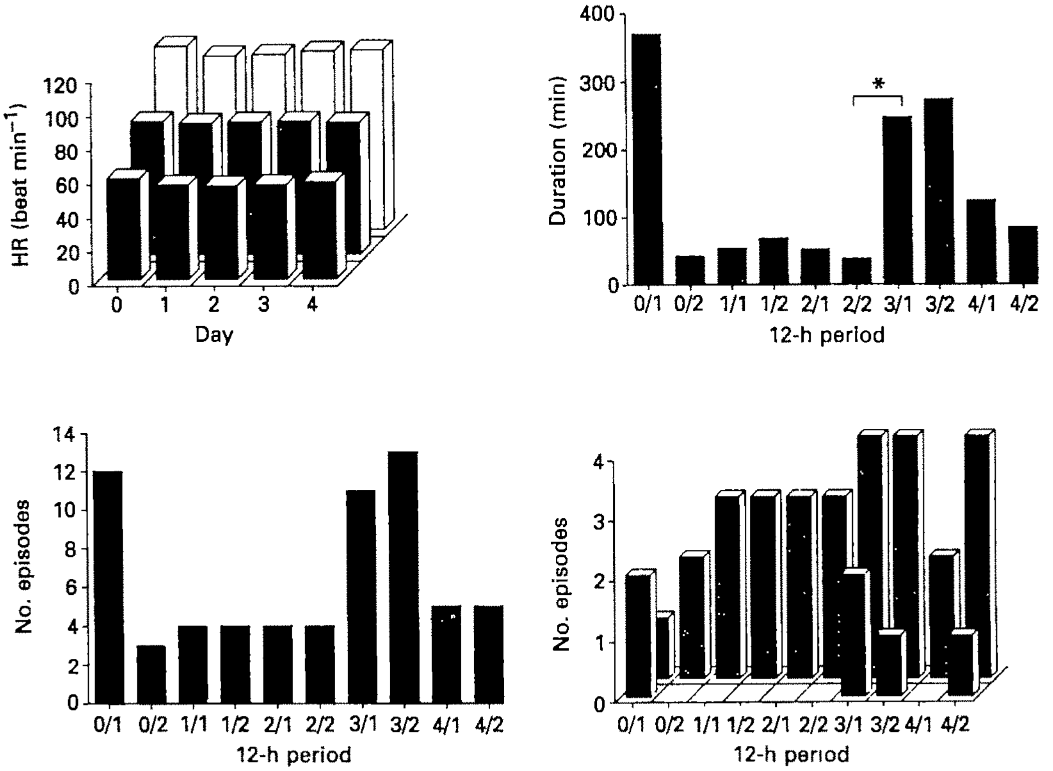

FIG. 1. Electrocardiographic data after surgery. Maximum (□), mean (▨) and minimum (■) heart rate (HR) in each 24-h period; duration, number and severity (▨ = 1–2 mm, ■ = > 2 mm) of ischaemic episodes in consecutive 12-h postoperative periods. *$P < 0.05$.

and recommenced as soon as possible after operation. Arterial pressure, a 12-lead resting ECG, cardiac enzyme and serum electrolyte analysis and chest x-ray were performed daily. Oxygen was given via a face mask continuously for the first 24 h and subsequently if indicated by blood-gas analysis.

We studied 15 patients (10 male), of mean age 67.3 yr. The mean interval between MI and surgery was 23.4 weeks. Eleven patients received a general anaesthetic and four a regional technique. No intraoperative or postoperative myocardial reinfarction was detected by the daily resting ECG recordings or cardiac enzyme concentrations. All patients were discharged from the hospital.

Ambulatory ECG data (fig. 1) show that the number, duration and severity of ischaemic episodes were greatest on the 1st and 3rd days after operation ($P < 0.05$ compared with day 2).

COMMENT

The peak incidence of perioperative MI is reported to occur on the day of operation and on the 3rd day after operation [2, 3]. The present study attempted to document the occurrence of myocardial ischaemia in patients who were at risk of postoperative reinfarction. Analysis of continuous ECG monitoring showed two periods when ischaemia was most prevalent. The duration, severity and number of ischaemic events was increased in the first 12 h after operation and in the periods corresponding with the 3rd day after operation compared with the 1st and 2nd days. Correlating the pattern of myocardial ischaemia with the individual course of the patients, we found only a few patients with frequent and severe ischaemic episodes immediately after operation. A greater number of patients, however, had relatively infrequent ischaemic events during the 7th and 8th measuring periods. This may suggest that the early ischaemic events are related to the operative procedure, whereas the second peak reflects non-specific phenomena, not related directly to intraoperative influences. London [3] observed that our knowledge of the many different factors involved in the pathogenesis of perioperative myocardial ischaemia and infarction remains incomplete and that the traditional simple concept of haemodynamic imbalance does not fit the complex pathophysiological derangements. Although haemodynamic, respiratory and coagulation changes occurred after operation in our small group of patients, they could not be correlated with the ischaemic events.

The results of this study confirm that symptomatic ischaemic events are rare, after both MI and surgery [1, 3, 4]. Only three of 65 ischaemic events in this study were symptomatic (4.6%). Asymptomatic ischaemia is not only a specific postoperative problem, it is also very common after MI. As many as 50% of the postinfarction patient population who have ST-segment changes on exercise testing are asymptomatic. However, the prognosis of patients after MI is worse if ST-segment changes can be detected by exercise testing or ambulatory ECG monitoring [1, 4].

Recent studies using modern Holter technology have documented ST-segment changes in the postoperative period of patients undergoing non-cardiac surgery, but only few studies extended over a longer postoperative period and none correlated ischaemic events between the postoperative days. Wong and colleagues [5] found ischaemic events throughout the first week, culminating on the 6th day after operation. Mangano and colleagues demonstrated that, in high risk patients undergoing non-cardiac surgery, postoperative myocardial ischaemia is an important correlate of adverse outcome [6]. The good outcome of our small group of patients despite severe ischaemia may have been influenced by the site and type of surgery and by left ventricular function. Only two patients had impaired left ventricular function with an ejection fraction of less than 40% and only three patients underwent upper abdominal or extended vascular surgery.

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COMPARATIVE EFFECTS OF PIPECURONIUM AND TUBOCURARINE ON PLASMA CONCENTRATIONS OF HISTAMINE IN HUMANS

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SUMMARY

We have examined the effects of a rapid bolus dose of pipecuronium 0.1 mg kg^{-1} or tubocurarine 0.5 mg kg^{-1} on plasma histamine concentration, heart rate and arterial pressure in 20 patients (n = 10 in each group). Anaesthesia was induced with thiopentone 6 mg kg^{-1} i.v. and maintained with 70% nitrous oxide and halothane in oxygen. Neuromuscular blocking drugs were administered 4 min after administration of thiopentone. Venous blood samples were obtained before induction, 1 min after thiopentone and 1, 3 and 5 min after the administration of the neuromuscular blocking drugs. Tubocurarine caused 240% and 210% increases in plasma concentration of histamine at 1 and 3 min, respectively. These changes were significant ($P < 0.05$) at 1 min and associated with a decrease in mean arterial pressure and an increase in heart rate. None of the 10 patients receiving pipecuronium had a significant change in plasma concentration of histamine or in haemodynamic variables.

KEY WORDS

Histamine plasma concentration. Neuromuscular relaxants · pipecuronium, tubocurarine.

Pipecuronium is a new long-acting, non-depolarizing steroid neuromuscular blocking drug which is devoid of cardiovascular effects [1]. The steroid muscle relaxants, unlike those which are structurally similar to tubocurarine, have been shown to cause only minimal release of histamine after administration of typical clinical doses [1]. Moss and colleagues [2] reported that the histamine-releasing property of tubocurarine occurred within the clinical dose range. In addition, a correlation exists between the extent of hypotension and the absolute concentrations of plasma histamine [2].

The development of a new radioenzymatic assay for histamine that provides improved sensitivity, specificity and reliability over previous assays [3], has greatly enhanced the ability to detect histamine in clinical settings.

This study was designed to examine the effects of a bolus dose of pipecuronium 0.1 mg kg^{-1} or tubocurarine 0.5 mg kg^{-1} on arterial pressure, heart rate and plasma concentration of histamine.

METHODS AND RESULTS

After Ethics Committee approval and informed consent, we studied 20 ASA group I or II unpremedicated patients allocated randomly to one of two groups ($n = 10$ in each). Any patient with recent exposure to antihistamine or antidepressant drugs was excluded from the study.

Before induction of anaesthesia, the radial artery was cannulated under local anaesthesia and heart rate and mean arterial pressure were monitored continuously. After insertion of an i.v. cannula in one arm and an additional cannula in the opposite forearm for sample collection, the first blood sample was obtained.

Anaesthesia was induced with thiopentone

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TABLE I. *Histamine concentrations and cardiovascular variables before and after administration of pipecuronium 0.1 mg kg^{-1} or tubocurarine 0.5 mg kg^{-1} (mean (SEM)). *P < 0.05 vs control values*

	Control	1 min after thiopentone	Time after blocking drug (min) 1	3	5
Histamine concn (pg ml^{-1})					
Pipecuronium (n = 10)	576.1 (113)	556.1 (95)	559 (88)	739.4 (146)	534.4 (104)
Tubocurarine (n = 10)	630.3 (76)	742.7 (90)	1511 (241)*	1367.1 (332)	981.8 (196)
Mean arterial pressure (mm Hg)					
Pipecuronium (n = 10)	84.7 (2.1)	80.3 (1.6)	79.4 (3.7)	79.9 (1.4)	80.4 (1.5)
Tubocurarine (n = 10)	84.4 (1.7)	80.7 (1.8)	73 (1.9)*	62.2 (2.4)*	64.4 (1.8)*
Heart rate (beat min^{-1})					
Pipecuronium (n = 10)	71.5 (1.8)	75.5 (1.5)	71.5 (1.7)	71.5 (1.9)	70.8 (1.8)
Tubocurarine (n = 10)	75.9 (2.5)	78.9 (2.2)	85.6 (1.9)*	88 (2.3)*	81.6 (1.9)

6 mg kg^{-1} i.v., and was maintained with 70% nitrous oxide and halothane in oxygen via a face mask.

A second sample of blood was obtained 1 min after injection of thiopentone. Three minutes later, a single bolus of pipecuronium 0.1 mg kg^{-1} or tubocurarine 0.5 mg kg^{-1} was administered over 5 s to patients in groups I and II, respectively. Samples 3, 4 and 5 were obtained 1, 3 and 5 min after administration of the neuromuscular blocker. Heart rate and arterial pressure were recorded at each sampling. Intubation of the trachea was performed after blood sampling.

Blood samples were collected in vacutainer tubes containing ethylenediaminetetra-acetate and placed immediately on ice. Cold centrifugation was performed rapidly, the plasma separated and frozen. The plasma samples were analysed by radioenzymatic assay. This technique is sensitive to 1–2 pg using a 25-μl sample [3]. The samples were assayed in duplicate, with duplicate internal standards.

Statistical analysis was performed by analysis of variance for repeated measures. If the hypothesis was rejected, individual comparisons were performed by Bonferroni adjusted paired t test. For all statistical comparisons, differences were considered significant when $P < 0.05$.

All results are expressed as mean (SEM). The two groups were comparable with respect to age, weight and gender. Mean ages were 27.5 (2.8) and 30.3 (2.9) yr, and mean body weights 67.9 (2.8) and 66.9 (2.6) kg in groups I and II, respectively. The male:female ratios were 6:4 and 7:3 in groups I and II, respectively.

The results are summarized in table I. Plasma histamine concentrations did not change significantly after administration of thiopentone. Administration of pipecuronium 0.1 mg kg^{-1} caused virtually no change in plasma concentration of histamine at any time. In contrast, in the tubocurarine group, the average peak plasma concentration of histamine increased by 240% at 1 min ($P < 0.05$) but, as in the case with other studies [2], there was a wide range in response, varying from 505.5 to 2589.3 pg ml^{-1}. A 210% increase in plasma concentration of histamine was noted at the 3-min sample in the tubocurarine group ($P > 0.05$). The increase in concentration of histamine at 1 min was significantly greater in the tubocurarine group (unpaired t test).

Administration of tubocurarine resulted in a significant increase in heart rate and decrease in mean arterial pressure. In six patients (60%) in this group, there were clinical signs of histamine release, with development of mild to moderate erythema over the trunk and face. None of the patients in the pipecuronium group had signs of histamine release or any haemodynamic changes of clinical or statistical significance.

COMMENT

We have demonstrated that administration of pipecuronium 0.1 mg kg^{-1} ($2 \times ED_{95}$) [4] was not associated with increased plasma concentrations of histamine or changes in haemodynamic variables. Tassonyi and colleagues [1] noted that the administration of pipecuronium in a dose as large as $3 \times ED_{95}$ (0.15 mg kg^{-1}) was accompanied by haemodynamic stability in patients undergoing coronary artery bypass grafting.

The doses of non-depolarizing neuromuscular blocking drugs selected in this study have clinical relevance, although they are not equi-effective. The tubocurarine dose selected (0.5 mg kg^{-1}) represents only 1 × ED_{95} [5].

Our data are consistent with those of Moss and colleagues [2], in that patients who received tubocurarine 0.5 mg kg^{-1} as a bolus had significant increases in plasma concentration of histamine and changes in haemodynamic variables. Although this haemodynamic response, which results from the release of endogenous histamine and reduction in postganglionic sympathetic activity, is probably of little clinical significance in the healthy patient, the effect may be more important in the patient who is hypovolaemic, or has cardiovascular disease. The haemodynamic effects may be minimized by slowing the rate of injection (thereby decreasing histamine release), or pretreating with histamine receptor (H_1 and H_2) antagonists [2]. Watkins, however, noted that release of histamine in concentrations of 1–2 ng ml^{-1}, as reported for tubocurarine in this study, produced only mild clinical effects which were usually harmless [6].

Administration of thiopentone did not result in any significant changes in plasma concentration of histamine (table I). This finding is in accordance with that reported by others [2].

In conclusion, the principal finding of this study was that administration of pipecuronium in a dose as great as 2 × ED_{95} did not result in any significant changes in plasma histamine concentration or in haemodynamic variables.

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THE LOADING DOSE IN CONTINUOUS INFUSION EXTRADURAL ANALGESIA IN OBSTETRICS

E. F. JANES AND J. W. McCRORY

SUMMARY

We have investigated the need for a loading dose of local anaesthetic before continuous extradural analgesia. After a standard test dose, patients received 0.08% bupivacaine 8 ml, isotonic saline 8 ml or nothing. A continuous infusion of 0.08% bupivacaine 20 ml h^{-1} was then commenced. The mean times to onset of satisfactory pain relief were similar in the first two groups, but prolonged significantly in the third. This group also required more interventions for inadequate analgesia, although not significantly so. Mean time to achieve highest level of block was significantly shorter in the first group.

KEY WORDS

Anaesthetics, local. bupivacaine. Anaesthetic techniques: extradural infusion, loading dose.

Continuous extradural infusion of local anaesthetic solution has become an acceptable method of pain relief in labour, several advantages being claimed in comparison with bolus administration [1, 2]. Most published accounts of this technique recommend that a loading dose of local anaesthetic (in addition to an initial test dose) be given before the infusion is started [1–3].

In a study by Ewan [3], 53% of hypotensive episodes occurred within 30 min of a loading dose of 0.5% bupivacaine 8 ml. Macleod obtained a smaller incidence, without significantly affecting onset of satisfactory analgesia, by using an equal volume of 0.08% bupivacaine [4]. In the latter study the amount of bupivacaine in the loading dose was small (6.4 mg) compared with that in the test dose (15 mg). The object of this study was to determine if such a loading dose contributes to the onset of analgesia by extra fluid volume or extra local anaesthetic.

METHODS AND RESULTS

The study was approved by the District Ethics Committee. Informed consent was obtained from all patients taking part. Sixty women requesting extradural analgesia during the first stage of labour were allocated randomly to one of three groups. The following exclusion criteria were applied: significant cardiovascular disease or hypertension requiring pharmacological control; antepartum haemorrhage; prior administration of opioids; cervical dilatation < 5 cm at the most recent vaginal examination.

An i.v. infusion of Hartmanns solution was commenced, but no fluid preload was given. The extradural space was identified at the level of the L2–3 interspace, using a 16-gauge Tuohy needle and a loss of resistance to air technique. An extradural catheter was passed cephalad, leaving 3 cm within the space after withdrawal of the Tuohy needle. The catheter was fixed in place and the patient placed in the semirecumbent wedged position.

A solution of 0.08% bupivacaine solution was prepared by dilution of 0.5% bupivacaine 8 ml in 0.9% saline to a volume of 50 ml.

All patients were given 0.5% bupivacaine 3 ml as a test dose, followed by 0.08% bupivacaine 1.5 ml in groups B and N, or 0.9% saline in group S, to flush the catheter and filter deadspace. After 5 min, accidental subarachnoid injection was excluded. This was followed by extradural administration of 0.08% bupivacaine solution 8 ml (group B); 0.9% saline solution 8 ml (group S); nothing (group N).

An extradural infusion of 0.08% bupivacaine 20 ml h^{-1} (delivered by electric syringe pump) was

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TABLE I. *Mean (range) times to onset of analgesia and to highest level of block, and number of interventions in the three groups*

	Group B	Group S	Group N
Number of patients	19	20	20
Time to onset of satisfactory analgesia (min)	12.7 (7–20)	13.3 (9–30)	24 (16–40)
Mean time to highest level of block (min)	33.7 (20–50)	46.5 (20–50)	53 (20–50)
Number with inadequate analgesia at 25 min	1	2	7
Number requiring intervention for hypotension	4	2	2

then started. After a further 20 min, an additional bolus of 0.08% bupivacaine 8 ml was given if the patient found the resultant analgesia inadequate. This was repeated 10 min later if analgesia was still inadequate.

After the test dose, heart rate and systolic and diastolic arterial pressures were measured using an automatic non-invasive recorder (Accutorr, Datex) at 1-min intervals for 5 min, at 5-min intervals for 25 min, and again at 1 h. The height of block was assessed by loss of cold discrimination using an ethyl chloride spray, and recorded at the same times as the cardiovascular variables. The severity of motor block was assessed using a four-point scale: 0 = no weakness; 1 = able to lift foot clear of bed; 2 = able to slide the foot up the bed; 3 = unable to slide the foot up the bed. The time to onset of satisfactory analgesia was recorded as the time from loading dose to the first non-painful contraction (in the patient's view). The study was concluded 1 h after administration of the test dose.

Parametric data were analysed using one-way analysis of variance. The quantity of non-parametric data was inadequate to permit analysis.

There were 19 subject in group B, 20 in group S and 20 in group N. One patient was excluded because of development of a unilateral block. There were no statistical differences between the groups in age, weight, height, parity or degree of cervical dilatation at the time of insertion of the extradural needle.

There was no difference between mean times to onset of satisfactory analgesia in groups B (12.7 min) and S (13.3 min), but onset in group N (24 min) was prolonged significantly in comparison with the two other groups ($P > 0.0001$).

In group N, seven patients (35%) required one intervention for inadequate analgesia, compared with one patient in group B (5%) and two in group S (10%) (table I). No patient required a second intervention. A greater number of patients in group B required intervention for hypotension (defined as a greater than 25% decrease in systolic arterial pressure) than in the two other groups. However, the total numbers of interventions for both pain and hypotension were too few to allow statistical analysis.

The maximum height of block produced was similar in all groups (T7), but the time to achieve that level of block was significantly shorter in group B in comparison with the two other groups ($P < 0.001$), between which there was no difference.

No patient in any group developed motor block of severity greater than 1 (subjective feeling of weakness) and there was no difference between the groups.

COMMENT

The results suggest that onset of analgesia is delayed when a test dose alone is administered in a continuous extradural infusion technique. This may be anticipated, as it has been shown that fluid infused at a rate of 10 ml h^{-1} may take 30 min to cover three lumbar segments [5]. Administration of a loading dose of 0.08% bupivacaine 8 ml significantly reduced the delay, but appeared to have no advantage compared with an equal volume of isotonic saline. It must be presumed that such a loading dose merely acts as a diluent for the local anaesthetic administered in the test dose, thereby "spreading" it within the extradural space. However, the extra local anaesthetic in the loading dose was not without effect, as a significant decrease in the time to achieve maximum block height was demonstrated. Dye injected into an established block has been shown to occupy the whole of the local anaesthetic sleeve present [5]. However, it has been suggested in a previous study [4] that the loading dose is "pushed" cephalad by the continuous infusion, so that a greater concentration reaches the upper thoracic segments. In that study, a reduction in time to achieve maximum block height was obtained when the loading dose of bupivacaine was increased from 8 ml of 0.08% to 8 ml of a 0.5% solution. It would appear that the amount of local anaesthetic in the loading dose is related inversely to the time to achieve maximum height of block.

In summary, a loading volume alone was necessary for acceptable onset of analgesia in a continuous extradural analgesia technique. Extra local anaesthetic decreased the time to achieve maximum block height, and increased the incidence of hypotension.

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HAEMODYNAMIC EFFECTS OF PERIODIC VENTILATION: ABOLITION WITH SUPPLEMENTARY OXYGEN

M. K. REEDER, M. D. GOLDMAN, L. LOH, A. D. MUIR AND K. R. CASEY

SUMMARY

A 63-yr-old man was noted to breathe with a periodic pattern of ventilation during sleep, both before and after operation for coronary artery grafting, and 6 weeks later after aortic aneurysm repair. Periodic ventilation was associated with cyclic oxygen desaturations and increases in heart rate and arterial pressure. Administration of oxygen was found to abolish consistently the periodic pattern and the associated haemodynamic changes.

KEY WORDS

Arterial pressure: fluctuation. Oxygen: therapy. Sleep· periodic breathing, oxygen desaturation.

Episodic decreases in arterial oxygen saturation (Sa_{O_2}) during sleep are common in both the early [1] and late postoperative periods [2], and are thought to be caused by obstructive or central apnoea and hypopnoea. In patients with obstructive sleep apnoea (OSA), increases in heart rate and arterial pressure accompany arousals and the release of episodic ventilatory obstruction [3]. The present report documents heart rate and arterial pressure fluctuations occurring with episodes of central apnoea in a patient with a periodic pattern of ventilation. We also describe the effect of supplementary oxygen on ventilatory pattern and haemodynamic changes.

PATIENT AND METHODS

During an investigation of pre- and postoperative arterial oxygen saturation in patients undergoing elective major abdominal vascular surgery, the patient was studied on two occasions. He was studied initially before and after coronary artery grafting, and again 6 weeks later, before and after aortic reconstructive surgery. On both occasions, pre- and postoperative Sp_{O_2} and heart rate were measured and displayed once every 1 s from an Ohmeda 3700 pulse oximeter, using a computer program designed for respiratory sleep studies. Respiratory monitoring on both occasions before and after operation used an Oxford Medical MPA portable sleep and respiration recorder with an oximeter, mercury-in-rubber strain gauges, and nasal and oral airflow thermistors.

On several nights after both surgical procedures, arterial pressure was measured non-invasively with a Finapres (Ohmeda), and the digital output of the Finapres (systolic, diastolic AP) was sampled each beat by a microcomputer, simultaneously with Sp_{O_2} data from the oximeter.

CASE REPORT

A 63-yr-old man (weight 70 kg, height 166 cm) was admitted for repair of an abdominal aortic aneurysm. He had no respiratory history of significance and did not snore heavily, although his wife reported that for years he had breathed heavily and deeply during sleep. He was mildly hypertensive, but not receiving medication. He had symptoms of effort-dependent chest pain and nocturnal angina. A preoperative radionuclide cardiac gated blood pool (MUGA) scan indicated an ejection fraction of 31 % and severe ischaemic heart disease. This was confirmed by angiography, and he underwent coronary artery grafting 6

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weeks before attempted aneurysm repair. For both procedures, the patient received a standard anaesthetic technique using fentanyl during operation, with an i.v. infusion of morphine for postoperative analgesia.

RESULTS

Preoperative recordings

A pattern of nearly symmetrical de- and resaturation and modest cyclic changes in heart rate typical of central apnoea was noted, with an apnoea/hypopnoea index of 69 per hour of sleep time, with a desaturation index of 54 per hour of study. Similar results were obtained before aortic aneurysm surgery.

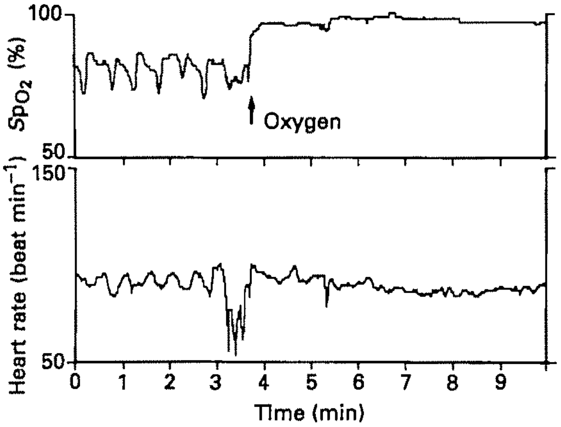

FIG. 1. Continuous tracing of Sp_{O_2} and heart rate during the 2nd night after operation. Administration of oxygen abolished desaturation and cyclic increases in heart rate.

Postoperative respiratory patterns

Following both surgical procedures, 50 % oxygen was given via a face mask. The first night was free from significant respiratory events. The following night (postoperative night 2) supplementary oxygen was discontinued. In addition to a baseline Sp_{O_2} of 85 %, there were episodic decreases in saturation to about 70 %, associated with increases in heart rate (fig. 1). Reinstitution of oxygen therapy prevented the desaturations and abolished the periodic increases in heart rate for the remainder of the night. During the 1-h period without supplementary oxygen, the patient suffered 62 episodes of apnoea, resulting in decreases in Sp_{O_2} to 70–75 %. There were three episodes of apnoea during the next 6 h of oxygen therapy. Comparable findings were recorded after aortic aneurysm repair.

Arterial pressure and periodic breathing

Figure 2 shows systolic arterial pressure and Sp_{O_2} on day 3 after aortic reconstructive surgery while the patient breathed room air and while he breathed oxygen 6 litre min^{-1} via face mask. Cyclic changes in arterial pressure occurred with each cycle of desaturation, with room air. With the increase in Sp_{O_2} after supplementary oxygen, periodic ventilation ceased and the arterial pressure pattern became more stable. Brief discon-

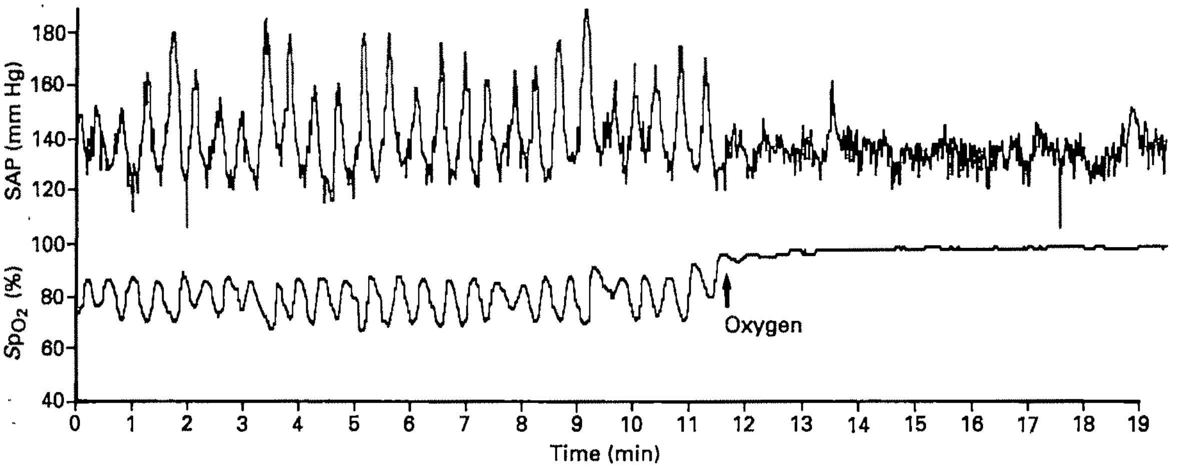

FIG. 2. Continuous recording of systolic arterial pressure (SAP) by Finapres, and Sp_{O_2}. Oxygen administration abolished the cyclical hypoxaemia and hypertension.

tinuation of oxygen resulted in the reappearance of the previous pattern. Identical findings were recorded after coronary artery graft surgery.

DISCUSSION

Abnormal patterns of ventilation (central or obstructive apnoeas, or hypopnoeas), are seen frequently in both the early and late postoperative periods [1, 2]. In patients undergoing major abdominal vascular surgery, we have frequently observed periodic breathing in the postoperative period. The cause of these patterns of breathing may be related to opioid sedation, hypoxaemia or decreased cardiac output and prolonged circulation time [4, 5]. Our patient's periodic ventilation before operation may have been a result of his reduced ejection fraction [4–6].

Periodic breathing occurs also during sleep in healthy individuals at high altitude [5]. In these individuals, administration of oxygen eliminates periodic breathing and is associated with a concomitant increase in Pa_{CO_2} [7]. Under hypoxic conditions, administration of carbon dioxide abolishes periodic breathing promptly. These chemoreceptor reflexes are likely also to become unstable if the circulation time from the lungs to the chemoreceptors is increased [5].

Arterial pressure fluctuations during obstructive sleep apnoea are well documented [8]. This case report demonstrates that, in our patient, periodic ventilation was accompanied also by cyclic increases in arterial pressure and heart rate. The mechanism for these periodic alterations in pressure is believed to arise from chemoreceptor stimuli, synchronous with those controlling respiration [9].

It is not certain if fluctuations in heart rate, arterial pressure and Sa_{O_2} accompanying periodic ventilation are harmful to patients with ischaemic heart disease. Cardiac work is increased in association with cyclic hypertension and it is of interest that this patient complained of nocturnal angina before coronary artery grafting.

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CONTROLLED HYPOTENSION FOR CEREBRAL ANEURYSM SURGERY IN THE PRESENCE OF SEVERE AORTIC COARCTATION

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SUMMARY

A patient is described with a bicuspid aortic valve and an undiagnosed aortic coarctation, presenting with a subarachnoid haemorrhage. A cerebral aneurysm was clipped under controlled hypotension. In view of the risk of inducing severe hypotension in the distal aorta in this patient, femoral arterial pressure was monitored. A marked reduction in the radial–femoral arterial pressure gradient during controlled hypotension was noted.

KEY WORDS

Anaesthesia: neurosurgical. Anaesthetic techniques: controlled hypotension. Heart aortic valve disease, coarctation of the aorta.

The association between coarctation of the aorta and cerebral aneurysm is rare, but well documented [1–4]. In such patients, the advantages of using controlled hypotension in clipping the aneurysm must be weighed against the risk of producing hypotension distal to coarctation, leading to spinal cord ischaemia.

A patient with this anomaly and a bicuspid aortic valve is described, in whom simultaneous radial and femoral arterial pressure monitoring was used to manage distal aortic perfusion pressure during clipping of a ruptured cerebral aneurysm.

CASE REPORT

A 33-yr-old female with a past history of hypertension, treated with metoprolol, and a congenital bicuspid aortic valve, was admitted to a provincial hospital with sudden onset of confusion and impaired consciousness, preceded by headaches for 1 week. Clinical examination revealed a drowsy but orientated patient, with neck stiffness and a dense left hemiplegia. Delayed femoral pulses were noted, as was rib notching on the chest radiograph, raising the suspicion of an aortic coarctation.

A lumbar puncture yielded uniformly blood-stained CSF and a CT scan confirmed a frontal midline subarachnoid haemorrhage. The patient was transferred to our institution for further investigation and management.

A cerebral angiogram attempted via the right femoral artery failed because of a complete aortic coarctation with large collaterals, just distal to the left subclavian artery. Angiography by the trans-axillary approach demonstrated a 5-mm anterior communicating artery aneurysm, and a smaller aneurysm at the bifurcation of the right middle cerebral artery. An echocardiogram suggested peak systolic gradients across the bicuspid aortic valve and the coarctation of 44 mm Hg and 56 mm Hg, respectively. Mild left ventricular hypertrophy was noted.

The patient was scheduled to undergo clipping of the anterior communicating artery aneurysm via a left frontal craniotomy in the supine position. All laboratory values were within normal limits. Premedication consisted of dexamethasone 4 mg and atropine 600 μg i.m. After induction of anaesthesia with thiopentone 250 mg, fentanyl 300 μg and atracurium 30 mg, anaesthesia was maintained with 60 % nitrous oxide and isoflurane in oxygen. Neuromuscular block was maintained with an infusion of atracurium. Mannitol 20 g and

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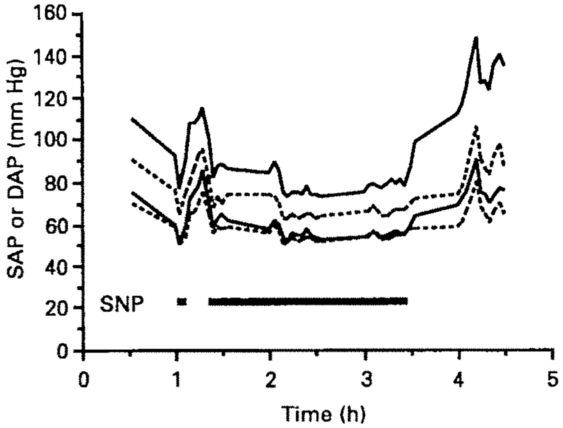

FIG. 1. Changes in radial (—) and femoral (– – – –) arterial systolic and diastolic arterial pressures throughout anaesthesia. SNP = Sodium nitroprusside infusion.

an infusion of propofol provided good surgical conditions. Controlled hypotension was produced with sodium nitroprusside (SNP).

Throughout anaesthesia, core body temperature, radial arterial pressure, arterial oxygen saturation, urine output and end-tidal carbon dioxide concentration (E'_{CO_2}) were monitored. Ventilation was controlled to maintain E'_{CO_2} at 3.5–4.0%.

Concern about distal aortic hypotension and spinal cord hypoperfusion prompted us to monitor femoral artery pressure during the procedure. This enabled direct comparison between radial and femoral arterial pressures (AP) during the hypotensive period, with transducers placed at the level of the carotid siphon.

Variations in radial AP were reflected in the femoral AP (fig. 1). Although there was a gradient of approximately 20 mm Hg between mean radial and femoral pressures during normotension, this decreased to 3–5 mm Hg during controlled hypotension. At no time did mean femoral AP decrease to less than 56 mm Hg. This finding, and a urine output of at least 70 ml h^{-1} throughout the case, suggested an adequate perfusion pressure in the distal aorta during hypotension of the upper body. It was noted that the respective diastolic arterial pressures were almost identical during controlled hypotension (fig. 1).

Following successful clipping of the aneurysm, the patient was transferred to the intensive care unit. After operation, her neurological status was unchanged, but episodic hypertension required therapy with i.v. hydralazine.

The patient was discharged 18 days after operation to a rehabilitation hospital, with plans to clip the second aneurysm at a later date. Her AP remained well controlled with metoprolol 100 mg twice daily.

DISCUSSION

The association between coarctation of the aorta and cerebral aneurysm was described first by Eppinger in 1871 [1]. In a literature review, Fukuda, Sako and Yonemasu found the incidence of coarctation among patients with cerebral aneurysms ranged from 0.19 to 1.9% [2]. The association appears more prevalent in young patients, however. Patel and Richardson [3] found that seven of 58 patients (12%) younger than 19 yr with subarachnoid haemorrhage had a coarctation, while Matson [4] found an incidence of three in 13 patients (23%) in a similar age group. A bicuspid aortic valve, as in the patient presented, may be expected to occur in 25–50% of patients with coarctation of the aorta [5]. Unfortunately, the coexistent coarctation may be overlooked. LeBlanc and colleagues [6] cited six cases of this combined anomaly, only one of which was diagnosed correctly at the time of admission. This presentation highlights the need to exercise a high index of suspicion of aortic coarctation in a young hypertensive patient presenting with a cerebral insult.

Our decision to use femoral arterial pressure monitoring as an index of spinal cord perfusion pressure was based upon the expectation of a significant decrease in distal aortic pressure during controlled hypotension. This technique has been practised in aortic coarctation repair as a means of objectively monitoring and managing distal aortic pressures during cross clamping, for prophylaxis of renal medullary ischaemia [7]. A mean distal aortic pressure in excess of 50 mm Hg has been suggested as compatible with adequate spinal cord perfusion [8]. Where circulation to the spinal cord may be compromised, Berendes and colleagues [9] have advocated that both femoral arterial and spinal fluid pressures be monitored, the difference representing the true perfusion pressure. During craniotomy, the CSF pressure is zero, making the latter measurement unnecessary in our patient.

Robine and co-workers [10] managed a 17-yr-old female with multiple cerebral aneurysms and aortic coarctation in a similar way. It was found that, with controlled hypotension, the gradient between mean radial and femoral AP decreased from 25 mm Hg to 5 mm Hg, but no explanation for this was offered.

In our patient, mean femoral AP approached mean radial AP as arterial pressure was decreased. This observation may be explained by an electrical analogy, visualizing the aorta as a fixed resistance (the coarctation) in parallel with a variable resistance (collaterals). During infusion of SNP, the collateral circulation dilates and the variable resistance approaches zero, reducing the pressure gradient across the aorta, regardless of the static nature of the coarctation. The inference from this is that, in a patient with poor collateral circulation, the distal aortic pressure may decrease markedly during controlled hypotension. The preoperative preparation must include an assessment of the adequacy of these collaterals, on clinical grounds (rib notching, chest wall bruits, poor femoral pulses) and angiographically.

An alternative explanation may lie in the effect of SNP on flow across the coarctation and collaterals. If the coarctation renders the lower body relatively ischaemic, with compensatory vasodilatation, during infusion of SNP the peripheral resistance of the lower body circulation may decrease to a lesser extent than that of the upper body circulation. In this case, for a given cardiac output, the flow across the coarctation/collateral complex may decrease with administration of SNP, with a reduction in the pressure gradient. The assumption in this hypothesis is that the collateral circulation is unresponsive to SNP and the resistance of the coarctation and collaterals remains fixed.

The place of evoked potential monitoring as an index of spinal cord integrity is unclear. Doyle [11] has indicated the potential for neurological damage in the absence of any electrophysiological change when using somatosensory evoked potentials. A likely explanation is that these potentials are monitors of posterior cord function, whereas the anterior cord is more at risk during episodes of hypotension.

In conclusion, this report emphasizes the importance of excluding aortic coarctation in young hypertensive patients with cerebral aneurysms. When controlled hypotension is indicated in patients in whom a coarctation of the aorta is present, a preoperative assessment of the collateral circulation assists in the identification of those at risk of spinal cord ischaemia. We suggest that femoral arterial pressure monitoring is a rational way of recognizing and managing distal aortic hypotension.

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COMPARTMENT SYNDROME AFTER PRESSURIZED INFUSION

M. D. TOBIAS, C. W. HANSON III, R. B. HEPPENSTALL AND S. J. AUKBURG

SUMMARY

We report two cases of compartment syndrome caused by extravasation of infused fluids and suggest a rationale for management and treatment based upon slit catheter monitoring of pressure in the compromised compartments.

KEY WORDS

Complications: compartment syndrome. Fluid balance: intravenous fluid administration.

Compartment syndrome is caused by any condition which increases interstitial pressure within a muscle compartment to the extent that blood flow is compromised. It is seen classically after trauma to an extremity with crush injury, vascular damage or subsequent tight bandaging. Its sequelae may include irreversible neural and muscular damage secondary to the ischaemic insult. Previously described iatrogenic causes of particular interest to anaesthetists include limb compression in the insensible patient [1], arterial cannula extravasation [2], hyperosmolar Bier block [3] and intra-arterial barbiturates [4]; these reports appear in orthopaedic surgery and neurology literature. Pressurized infusions through infiltrated i.v. catheters represent a potential source of compartment syndrome with resulting dysfunction [2, 5, 6].

We report two cases of compartment syndrome caused by extravasation of infused fluids and suggest a rationale for management and treatment based on monitoring of pressure in the compromised muscle compartments with a slit catheter.

CASE REPORTS

Patient No. 1

An 81-yr-old female was admitted to the Accident and Emergency department after a low velocity motor vehicle accident in which she suffered injuries to the body and head, with loss of consciousness. A CT scan of the head and abdomen revealed a subdural haematoma and retroperitoneal bleeding. When the patient's arterial pressure decreased from the admission value of 180/100 mm Hg to 90/60 mm Hg she was subjected to concurrent emergency craniotomy and exploratory laparotomy. Standard monitoring included ECG, pulse oximetry, capnography, oesophageal temperature and auscultation. A 20-gauge radial artery catheter and a 16-gauge i.v. catheter were placed in the right forearm. An 8.5-French gauge catheter was placed in the left antecubital fossa by a modified Seldinger technique. Anaesthesia was induced with fentanyl 15 $\mu g\ kg^{-1}$ and pancuronium via the right forearm i.v. catheter. After the abdomen was opened, the patient's arterial pressure decreased to 70/30 mm Hg. Three units of packed cells were administered rapidly through the catheter in the left antecubital fossa and dopamine was infused via the right forearm to maintain the systolic pressure at approximately 100 mm Hg. When a roller pump for rapid infusion was connected to the 8.5-French gauge catheter in the left arm, the perfusionist reported that the delivery pressure exceeded 30 mm Hg. Investigation revealed tense swelling of the left arm. An alternative i.v. route was obtained in the right arm and the remainder of the case was uneventful.

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After operation, slit catheters (Stryker) placed in the left arm by an anaesthetist revealed interstitial pressures (ISP) of 38 mm Hg in the biceps brachii compartment, 28 mm Hg in the triceps compartment, 28 mm Hg in the volar forearm compartment, and 25 mm Hg in the dorsal forearm compartment. Concurrent mean arterial pressure was 83 mm Hg. Fasciotomy was deferred in favour of conservative therapy. The patient's left arm was elevated and interstitial pressure monitoring was continued. The left biceps compartment ISP returned to 4 mm Hg approximately 24 h later.

Patient No. 2

A 77-yr-old man was admitted to hospital for elective repair of a symptomatic abdominal aortic aneurysm. In the operating theatre, initial monitoring comprised ECG, non-invasive arterial pressure and pulse oximetry. A radial arterial catheter and a 14-gauge antecubital fossa catheter were placed in the left upper extremity. An 18-gauge i.v. catheter was inserted into the right hand. A pulmonary artery catheter was advanced to wedge position via an introducer sheath in the right internal jugular vein.

Anaesthesia was induced with i.v. fentanyl 10 $\mu g\ kg^{-1}$ followed by pancuronium via the catheter in the right hand and maintained with nitrous oxide and isoflurane. The patient's left arm was placed at his side to facilitate positioning of a surgical retractor.

Fluids were allowed initially to flow into the left antecubital i.v. catheter by gravity but later, as blood loss increased, were infused under pressure. A total of 3 units of packed red blood cells, crystalloid 2 litre and starch solution 500 ml were infused through the catheter; no difficulties were noted by the anaesthetist. Approximately 90 min after surgical incision, the anaesthetist had difficulty obtaining an accurate arterial wave form and in withdrawing blood from the left radial artery cannula. Investigation revealed that the left arm was mottled and tense from the wrist to the border of the left pectoralis muscle. A presumptive diagnosis of compartment syndrome was made and all infusions to the left arm were discontinued.

A pulse oximeter probe placed on one of the digits of the left hand showed a saturation of 100% and good correlation of the pulse rate with the electrocardiograph heart rate. Distal pulses in the left arm were palpable. Slit catheter monitoring (Stryker) was established and showed interstitial pressures of 23 mm Hg in the dorsal forearm compartment and 34 mm Hg in the triceps compartment. The biceps brachii compartment pressure was 26 mm Hg and the forearm volar compartment pressure 15 mm Hg. Simultaneous mean arterial pressure was 110 mm Hg.

The procedure was concluded uneventfully, and the arm was treated conservatively, with ice, elevation and topical agents to an area of epidermolysis which developed over the antecubital fossa. The swelling resolved, and the patient suffered no permanent muscular, neural or epidermal sequelae.

DISCUSSION

Compartment syndrome occurs when diminution of blood flow is sufficient to cause ischaemic damage to neurovascular and muscular components. The full syndrome, as described by Richard Von Volkmann in 1881, includes paralysis and post ischaemic contractures. These late sequelae are now seen infrequently because surgical fasciotomy is performed usually as soon as compromise is suspected. While normal interstitial pressure is approximately 2–5 mm Hg, there is no absolute measured interstitial pressure at which fasciotomy is indicated. The decision to perform fasciotomy should be based upon the perfusion pressure (ΔP) of the compartment [7]—the difference between the mean arterial pressure and the interstitial pressure, and a major determinant of oxygen delivery. Phosphorus-31 NMR spectroscopy has been used to determine the perfusion pressure at which anaerobic metabolism begins in resting canine muscle [7, 8]. Aerobic metabolism ceases when the perfusion pressure is less than 30 mm Hg in normal muscle or 40 mm Hg in traumatized muscle. These perfusion pressures are the accepted thresholds for decompressive fasciotomy. The venous $P\text{O}_2$ at these perfusion pressures is approximately 1.4 kPa, reflecting increased oxygen extraction [9], and is the threshold for injury to capillary endothelium [10]. Endothelial injury tends to widen the area of ischaemia by augmenting oedema formation, thereby further decreasing perfusion pressure. This cycle of ischaemia and oedema is characteristic of the compartment syndrome. Surgical fasciotomy increases perfusion pressure by decreasing interstitial pressure to near atmospheric pressure.

Infiltration of i.v. catheters occurs often, but usually the driving force is gravity alone. Although anaesthetists frequently infuse fluids under pressure, only one report of compartment syndrome secondary to infiltration of a pressurized transfusion was found in the anaesthesia literature [6]. With the marked increase in the amount of blood and blood products being transfused under pressure in emergencies, this cause of compartment syndrome may become more common. The 8.5-French gauge untapered catheter, designed to give maximal flow by maximizing diameter, may distend fragile veins and predispose to rupture during cannulation or transfusions under pressure.

If large quantities of fluid are infused inadvertently into muscle compartments, slit catheters should be placed in the affected compartments. The technique for insertion of this device is simple. With a 14-gauge plastic i.v. catheter used as an introducer, the slit catheter is threaded into a muscle belly of the affected compartment. The slit catheter is connected to a low compliance transduction system. All air bubbles must be removed carefully or flushed from this relatively low pressure transducer system. The slit catheter provides more accurate intracompartmental pressures than transduction of the i.v. catheter. Transduction of the slit catheter signal may be performed with any standard pressure monitor. Specially designed monitors are manufactured by Stryker Surgical. The arterial and compartmental pressures used to calculate the perfusion pressure should be transduced with a common zero reference point. Fasciotomy should be considered if the perfusion pressure remains less than 30 mm Hg for more than a few minutes.

In the two cases presented, the perfusion pressures were well above the established threshold at which tissue damage ensues. Fasciotomy was avoided with little risk of further tissue damage.

In order to reduce iatrogenic complications, transfusion catheters should be placed in readily observable places, and re-evaluated when increased resistance to inflow is noted. Intermittent monitoring of transfusion catheter pressure may alert the anaesthetist to this hazard. If inadvertent extravasation of infusion substances occurs and fasciotomy is considered, slit catheter monitoring may help to direct rational therapy.

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BACKACHE AFTER EXTRADURAL ANAESTHESIA IN THE POSTPARTUM PERIOD: DISSECTION OF THORACIC ANEURYSM

Y. J. KAO, F. G. ZAVISCA, J. M. TELLEZ, R. G. NORTON AND G. B. RACZ

SUMMARY

We describe a case of postpartum ruptured dissecting aneurysm of the thoracic aorta, unrelated to the anaesthetic management with extradural anaesthesia. This complication is discussed in detail, as the anaesthetist may be the specialist required to respond to the common presenting symptom of severe back pain.

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques extradural Complications. back pain, thoracic aortic aneurysm.

Back pain after extradural anaesthesia is common in obstetric patients [1]. The incidence of back pain in the immediate postpartum period is similar after delivery regardless of the technique of pain relief [2] and the majority of patients respond to symptomatic management. However, before symptomatic therapy is prescribed, several rare but potentially catastrophic diagnoses must be excluded, including extradural haematoma, extradural abscess and dissection of thoracic aorta aneurysm.

Dissection of the thoracic aorta during pregnancy and in the postpartum period is a rare complication. The mortality has been reported to be 19–90 % [3–5]. However, these data originated before 1960, when dissection of the thoracic aorta was not amenable to surgical repair. Since then, advances have led to a survival rate of greater than 80 % after surgical repair of thoracic aortic aneurysms [6]. The rarity of this complication in pregnancy makes a high index of suspicion essential in making an early diagnosis.

Recently, we encountered a patient with a ruptured dissecting aneurysm of the thoracic aorta in the postpartum period after she received extradural anaesthesia. While anaesthetic management was unrelated to this complication, nevertheless we were consulted for her severe back pain.

CASE REPORT

A 23-yr-old parturient (gravida 2, para 1) was admitted after 41 weeks of normal gestation for induction of labour. During her first pregnancy, Caesarean section had been performed because of failure of labour to progress. On this occasion, labour was induced by amniotomy, followed by an infusion of oxytocin. On admission, her vital signs and laboratory tests were unremarkable, and haemoglobin was 13.5 g dl^{-1}. A lumbar extradural anaesthetic was administered, using 0.5 % bupivacaine 5 ml followed by an infusion of 0.125 % bupivacaine 10 ml h^{-1}. Analgesia was initially incomplete and the extradural catheter was resited. After 14 h of adequate extradural anaesthesia, progress of labour was poor; therefore, Caesarean section was performed. Because extradural anaesthesia at that time was judged to be inadequate for surgery, general anaesthesia was induced with thiopentone, followed by suxamethonium, and was maintained with nitrous oxide and enflurane in oxygen. Caesarean section and the immediate postoperative recovery were uncomplicated. During labour, general anaesthesia and the immediate postoperative period,

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there were no excessive or prolonged periods of hypertension or tachycardia. Twenty-four hours after operation, haemoglobin was 11 g dl^{-1}.

On the morning of the 3rd day after operation, the patient complained of severe back pain in the lower thoracic area, radiating to her right leg. Before the anaesthesist could be contacted for an opinion, the patient suffered a grand mal seizure, followed by ventilatory arrest and loss of peripheral pulses. The cardiopulmonary resuscitation team (with an anaesthetist member) was summoned.

After receiving ventilatory support with a bag and mask for several minutes, the patient regained consciousness. Arterial pressure at that time was 110/60 mm Hg, with a heart rate of 160 beat min^{-1}. With the patient receiving oxygen 10 litre min^{-1} via nasal cannulae, arterial blood-gas analysis revealed pH 7.34, P_{O_2} 24.4 kPa and P_{CO_2} 3.2 kPa. Chest x-ray demonstrated opacification of the left hemithorax and a rightward shift of the mediastinum. The patient was extremely anxious, complained continuously of severe interscapular pain and was transferred to the surgical intensive care unit where the haemoglobin concentration was found to be 6.1 g dl^{-1}. This was treated with a transfusion of packed red cells. Shortly after admission to the unit, the patient suffered another seizure, followed by cardiac arrest. A chest tube was inserted into the left hemithorax, which was followed immediately by draining 900 ml of bright red blood. Cardiopulmonary resuscitation consisted of external cardiac massage, ventilatory support via a tracheal tube, and an infusion of adrenaline. During the next 30 min, the patient was given 5 units of packed red blood cells and crystalloid solution 5000 ml. Her systolic arterial pressure (measured by automatic pressure monitor) could not be maintained greater than 60 mm Hg. The patient was taken to the operating theatre while still undergoing cardiopulmonary resuscitation. No invasive monitors could be placed and left thoracotomy was performed and revealed a ruptured dissecting aneurysm of the descending aorta. The aorta was cross clamped and internal cardiac massage was initiated. However, in spite of all efforts at resuscitation, the patient developed ventricular fibrillation and died.

Postmortem revealed a dissecting thoracic aortic aneurysm which commenced in the descending aorta just distal to the junction of the left subclavian artery. There was also a large mediastinal haematoma.

DISCUSSION

The relationship between extradural anaesthesia and long-term backache after childbirth has been examined recently in a large retrospective study. Patients who have had extradural anaesthesia have twice the incidence of backache compared with those who did not have an extradural (18.9% *vs* 10.5%) [1]. However, in another study, the incidence of backache was not related to extradural anaesthesia; with either regional or general anaesthesia, 30–40% of obstetric patients complained of back pain [7]. Patients who have extradural anaesthesia are often certain that back pain was caused by the extradural, despite assurances to the contrary [8]. Fortunately, the great majority of postpartum back pain responds to symptomatic management, but in treating postpartum back pain, potentially catastrophic diagnoses such as extradural abscess, extradural haematoma or dissection of thoracic aorta must be eliminated.

Dissection of the thoracic aorta may involve either the ascending or descending portions of the aorta, or both, and have been classified into three types by De Bakey and colleagues [9]: type I and type II arise at the ascending aorta and type III at the descending aorta. Only about 20% of aortic dissection are classified as type III. When complications and management are considered, types I and II may be grouped together, collectively termed type A; type III is also termed type B [10].

Most patients suffering from thoracic aortic aneurysm are elderly males with atherosclerosis and hypertension. However, congenital anomalies such as bicuspid aortic valve and coarctation of the aorta, Marfan's and Ehler–Danlos syndromes and syphilitic aortitis, also are associated with increased incidences of thoracic aortic aneurysm. It is generally accepted that degeneration of the tunica media of the aorta (Erdheim's medial necrosis) is one of the primary causes of thoracic aortic dissection.

In recent years, dissecting thoracic aortic aneurysm has been managed both medically and surgically [11]. Type I and type II dissections of the aorta are associated with cardiovascular (aortic regurgitation, pericardial tamponade, obstruction of major branch arteries at the arch), respiratory (compression of a main stem bronchus or trachea) or neurological (laryngeal nerve compression, central nerve system ischaemia) manifestations. In such cases, immediate surgical intervention may

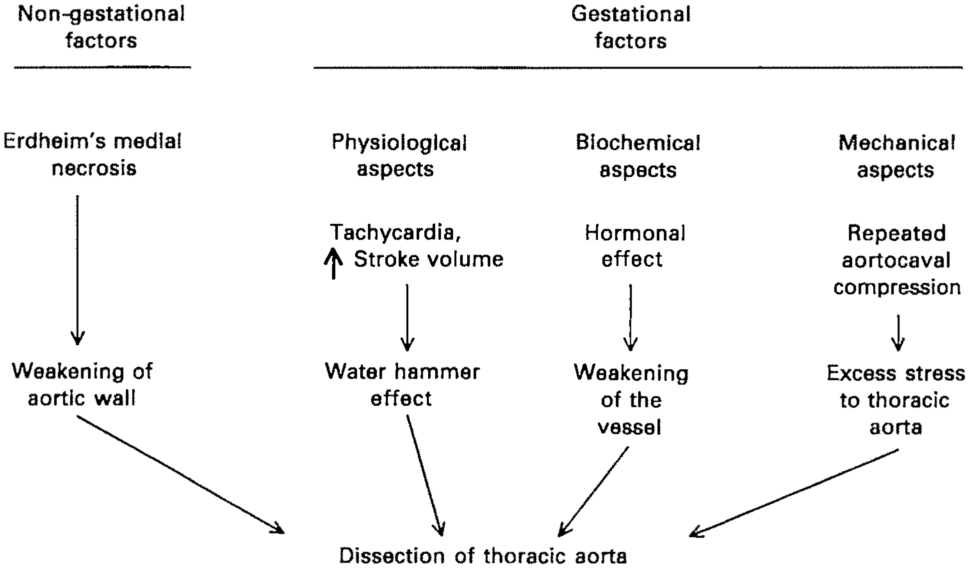

FIG. 1. Cardiovascular changes that probably contribute to the dissection of thoracic aorta during pregnancy.

be necessary. In contrast, type III dissections of the aorta are frequently asymptomatic and show less tendency to rupture. Treatment, therefore, is generally conservative. Beta-adrenergic blockers are used to reduce cardiac output and vasodilators to reduce the usually increased arterial pressure. Surgery may be performed electively [12, 13].

Dissection of the thoracic aorta associated with pregnancy may not be associated with hypertension [4]. Physiological, biochemical and mechanical changes that are associated with pregnancy and delivery and which may contribute to dissection are shown in figure 1. The hyperdynamic cardiovascular state of pregnancy may be a risk factor, as dissections of the aorta occur predominantly during the puerperium, when circulatory stress is maximal. Other factors related to pregnancy, such as hormonal changes, may also be important in weakening the aorta. However, in light of conflicting reports on histological changes of the aorta during pregnancy, this speculation remains controversial [14, 15]. The effect of repeated thoracic aortic pressure load increase induced by repeated compression of the abdominal aorta during pregnancy may also contribute to stretching a weakened thoracic aorta. This is supported by the observation that aortic aneurysms associated with pregnancy do not occur in the abdominal aorta [16].

Diagnosis of acute dissection of the aorta during pregnancy depends on clinical observation and a high index of suspicion. New and different patterns of radiating pain are the most consistent signs, and are often described as tearing or ripping in nature. The location of the pain usually indicates the origin of the dissection. Aneurysms of the ascending aorta are associated with anterior chest pain, whereas those of the descending aorta are associated with interscapular or lower thoracic back pain. The pain radiates to the upper or lower extremities as the dissection extends along the aorta and its branches. Changes in arterial pressure are not consistent, but the heart rate is almost always increased. Dyspnoea occurs frequently, caused by pain, or by the direct compression of the major airways by the expanding aneurysm. The haemoglobin concentration usually does not change initially, but a progressive decrease may occur later as a result of sequestration of erythrocytes by the aneurysm. Chest x-ray may reveal a widening of the mediastinum or haemothorax. Aortography establishes the definite diagnosis.

Both medical and surgical management of thoracic aortic dissection are complicated by gestation. A case of thoracic aorta aneurysm with successful obstetric and surgical management has been reported [17]. In less complicated dissections, when other organ systems are not compromised, β-adrenergic blockers and vasodilators may be used to maintain a normal or slightly reduced arterial pressure. Lumbar extradural anaesthesia may be used for management of labour and for control of arterial pressure. Halothane has been recommended as the agent for general anaesthesia [17, 18]. After stabilization of the aortic dissection and delivery of the fetus, surgical repair of the aneurysm may be undertaken. Cardiopulmonary bypass is used during repair of type A aneurysms.

In an acute situation, when the patient is experiencing a rapidly extending dissection with the acute onset of aortic insufficiency, cardiac tamponade, occlusion of major arterial branches, embarrassment of respiration or rupture of the aneurysm (as in the present case), surgical intervention offers the only hope for survival. If the aneurysm is not yet ruptured, induction of anaesthesia should be carried out with the patient prepared for immediate surgery. Blood and fluid should be readily available, along with multiple large-bore i.v. cannulae inserted in preparation for the need of rapid blood transfusion. For type I and type II aneurysms, femoral arterial–femoral venous partial bypass under local anaesthesia is an option [18, 19]; this reduces the severity of the consequences of lacerating the ascending aortic aneurysm during sternotomy.

If the aneurysm has already ruptured before incision, fluid resuscitation and immediate control of the aorta are priorities (as in the present case). Under such conditions, ruptured thoracic aortic aneurysm carries a grave prognosis. In one study of all patients with traumatically ruptured thoracic aortic aneurysm arriving alive at hospital, only 15% survived [20]. Presumably, the prognosis of ruptured thoracic aneurysms in the pregnant patient is similar.

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DILUTIONAL HYPONATRAEMIA FOLLOWING TRANSURETHRAL OPERATION FOR CLOT RETENTION

R. G. HAHN

SUMMARY

Dilutional hyponatraemia with symptoms (TUR syndrome) may occur not only in association with transurethral prostatic resection, but also in other operations in which electrolyte-free irrigating fluid is used. This case report describes a patient who developed the TUR syndrome after blood clots had been removed from the bladder with the aid of a transurethral resectoscope.

KEY WORDS

Complications: dilutional hyponatraemia. Surgery: transurethral.

CASE REPORT

An 82-yr-old man, who had previously undergone open prostatectomy, presented with voiding difficulties. His only medication was warfarin, which had been prescribed because of transient episodes of cerebral ischaemia. Cystoscopy revealed an urethral stricture and some remaining adenomatous prostatic tissue. On two occasions, the stricture was dilatated under local anaesthesia. Four days after the second dilatation, the patient developed acute urinary retention and suprapubic drainage was performed. There appeared to be a large amount of blood clot in the bladder, and it was decided to perform a transurethral blood clot evacuation procedure.

Atropine 0.25 mg i.v. was given and general anaesthesia was induced with diazepam 5 mg. Anaesthesia was maintained using a Bain circuit with a fresh gas flow of 67% nitrous oxide in oxygen at 7.5 litre min^{-1} and 0.75 % isoflurane. Isotonic crystalloid solution 1 litre and 5 % glucose solution 500 ml with sodium 80 mmol were given during the operation. The urologist evacuated blood clots and coagulated bleeding vessels via a resectoscope. Glycine 2.2 % in water was used to irrigate the bladder.

During the last 25 min of the procedure, which lasted for 75 min, the systolic arterial pressure increased from 110 to 150 mm Hg; heart rate was unchanged. After operation, the systolic pressure increased further to 200 mm Hg. The patient became confused and drowsy, and it was difficult to maintain an airway. Ninety minutes after operation, blood-gas analysis (whilst oxygen 4 litre min^{-1} was given via a nasal catheter) showed Pa_{O_2} 14.5 kPa, Pa_{CO_2} 5.5 kPa, pH 7.26, standard bicarbonate 18 mmol litre^{-1} and base excess -8 mmol litre^{-1}. The serum concentration of sodium had decreased from 141 to 116 mmol litre^{-1} during the operation. The diagnosis of transurethral prostatic resection syndrome (TUR syndrome) was made.

The patient was treated with i.v. infusion of 2 % saline solution 500 ml, 200 ml of bicarbonate 0.6 mol litre^{-1}, and frusemide 40 mg. His mental functions improved slowly. However, repeated volumetric fluid balance calculations suggested that no diuresis had been induced. From immediately before the operation to 6 h after, serum creatinine concentration increased from 148 to 208 μmol litre^{-1}, and urea concentration from 10.4 to 21.2 mmol litre^{-1}. Serum concentration of sodium was still reduced (119 mmol litre^{-1}). However, a second dose of frusemide (80 mg), administered 12 h after operation, induced diuresis and during that night the patient passed urine 2 litre in excess of his fluid intake. By the next morning, serum concentration of sodium had returned to normal (135 mmol litre^{-1}), but the serum concentrations of creatinine and urea remained increased for 5 days after operation (maximum 201 μmol litre^{-1} and 21.9 mmol litre^{-1}, respectively). The patient made a full recovery.

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DISCUSSION

Massive absorption of irrigating fluid may be prevented by placing the irrigating fluid bags no higher than 60 cm above the patient, and by limiting the duration of operation to no more than 1 h [1]. The volumes of irrigating fluid used and recovered should be compared if there is any suspicion of fluid absorption. Blood loss, serum concentration of sodium and osmolality should also be measured frequently. Hyponatraemia is a specific sign of fluid absorption, while a decrease in serum osmolality indicates that severe symptoms are likely to ensue [2]. Furthermore, at this hospital we often use an irrigating fluid containing both glycine and ethanol, which allows absorption to be monitored by means of expired breath analysis [3]. Unfortunately, none of these precautions was used during the operation described here. We were not aware of the possibility of dilutional hyponatraemia in association with evacuation of blood clot.

For many years, dilutional hyponatraemia resulting in circulatory and neurological symptoms (TUR syndrome) was thought to be a complication arising exclusively in connection with transurethral resection of the prostate. However, during the 1980s it has been apparent that the TUR syndrome may occur also after several other surgical procedures, such as percutaneous ultrasonic lithotripsy [4, 5], vesical ultrasonic lithotripsy [6] and intrauterine endoscopic laser surgery [7]. The present report is the first to describe dilutional hyponatraemia after operation for clot retention.

The signs and symptoms of TUR syndrome in this case were consistent with those known to occur in association with transurethral prostatic resection [1, 2]. The patient developed hypertension and encephalopathy, which remained unexplained until we received the results of serum sodium analysis. Blood-gas analysis showed metabolic acidosis, which is a common finding in TUR syndrome. In spite of treatment with hypertonic saline and bicarbonate, the patient suffered renal damage. The urinary excretion of water was low or absent during the first 8 h after operation, and the serum concentrations of urea and creatinine were increased.

In some washout procedures, normal saline may be used to irrigate the bladder. However, coagulation of bleeding vessels is often carried out, and a non-electrolyte irrigating fluid should be used. In transurethral prostatic resection, TUR syndrome results from absorption of electrolyte-free irrigating fluid through prostatic veins severed by the resectoscope. Another possibility is that the fluid is absorbed via open perforations in the prostatic capsule (extravasation). In our patient, the irrigating fluid was absorbed probably through the bleeding blood vessels responsible for clot retention. This case, together with other reports [4–7], draws attention to the possibility of TUR syndrome whenever electrolyte-free irrigating fluids are in contact with body surfaces damaged by surgery or injury.

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AURA: A NEW RESPIRATORY MONITOR AND APNOEA ALARM FOR SPONTANEOUSLY BREATHING PATIENTS

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SUMMARY

Previous attempts to introduce non-invasive monitoring of ventilation of spontaneously breathing patients into routine practice have been unsuccessful. The Aberdeen University Respiratory Alarm (AURA) allows such monitoring by utilizing the pyroelectric property of polarized polyvinylidine fluoride sensors to detect temperature changes that occur during breathing into an oxygen delivery face mask. A quartz crystal oscillator generates pulses that allow measurement of interexpiratory time and ventilatory frequency. The system incorporates LED digital displays, a bargraph and audiovisual alarms. An analog output permits display and analysis of the sensed signals. AURA performed satisfactorily in both volunteer studies and six patients in the clinical setting. AURA may be an appropriate respiratory transducer in those patients requiring oxygen therapy.

KEY WORDS

Equipment: respiration monitor. Monitoring: spontaneous breathing

Standards for monitoring during anaesthesia and in the recovery period have received increasing attention in recent years [1–4]. Unfortunately, all currently available anaesthetic techniques leave the patient at risk of respiratory depression which may extend well into the postoperative period as efforts are made to maximize patient analgesia and comfort. Although a useful monitor of tissue oxygenation, pulse oximetry has several limitations as a monitor of respiratory depression and apnoea [5].

Several techniques have been developed to solve the difficult task of monitoring ventilation in the spontaneously breathing patient [6–16]. However, to date there are few convenient non-invasive techniques available to measure and display routinely breath-to-breath variability or to allow early detection of apnoea in spontaneously breathing patients at risk.

The Aberdeen University Respiratory Alarm (AURA) [17] is a respiratory monitor and apnoea alarm system for spontaneously breathing patients receiving supplementary oxygen via a face mask. AURA measures and displays ventilatory frequency in breaths per minute and interexpiratory time in seconds. It has been designed to be non-invasive, incorporated within the most common means of oxygen administration and reliable in the presence of both patient movement and variable gas flows.

METHODS

The AURA system is based on three modules: sensor, timing and display. Figure 1 illustrates the interrelationships of these modules in a functional block diagram. A transformer-coupled power supply with a distribution board form an integral part of the system within a single housing. The sensor material used was polarized polyvinylidine fluoride (PVDF) which has both piezo- and pyroelectric properties [18]. Two PVDF sensor strips are mounted on the inside of an oxygen face mask (fig. 2) in a differential configuration so that the output of one sensor is compared with the output of the other. A difference in temperature

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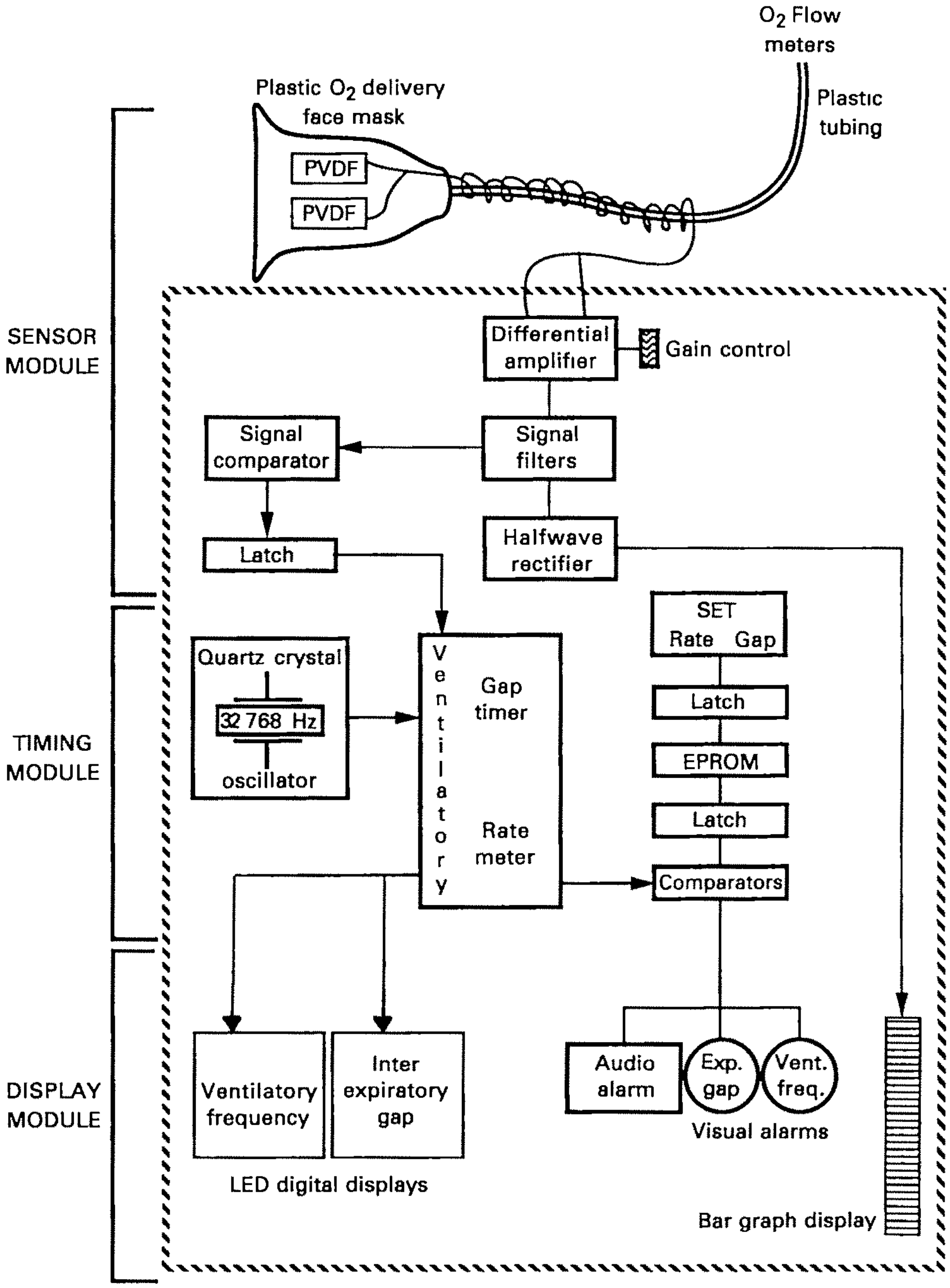

FIG. 1. Functional block diagram of the AURA system (power supply not shown).

between the two surfaces of each PVDF strip results in the development of a potential difference that is directly proportional to the rate of change of temperature. PVDF has low water absorption characteristics, easy configuration and is chemically inert.

The sensed signals are filtered, a.c.-coupled to a differential amplifier and subsequently undergo further filtering. A gain control permits adjustment of these signals, which are buffered to a bargraph display and compared with a precision reference voltage before being latched. The timing

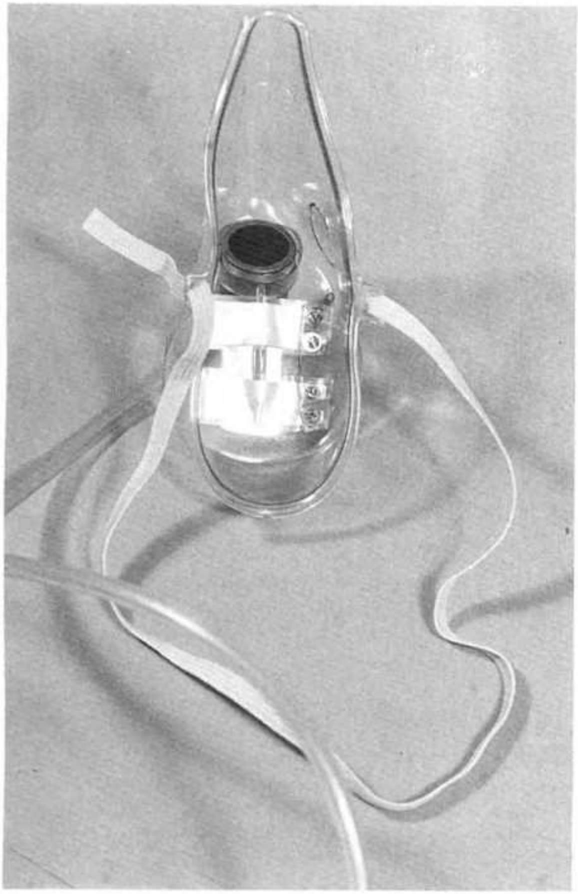

FIG. 2. Internal view of a modified oxygen delivery face mask with its PVDF sensors.

module consists of a 32768-Hz quartz crystal oscillator which generates pulses that are divided down to a number of reference frequencies, permitting measurement of the interexpiratory time (IET) and rate (*f*) and refreshing the digital displays. The timing module also drives the logic associated with the system. Two banks of switches govern EPROMS that allow the user to set the timing of alarms for *f* and maximum IET. The display and alarm modules include the logic to drive and respond to the alarm signals generated by the system.

The displays include: a bargraph and a soft audible click with each expiration, a double digit LED display of *f* and IET. A single audio alarm, and two red LED indicate the cause of the alarm. An analog output allows display and further analysis of sensed signals by a microprocessor. Before use, alarms are selected and checked. The mask is then applied to the face and the gain adjusted until the signal is optimal as indicated by the bargraph display.

Initial evaluation of AURA as a monitor of ventilation was carried out in volunteers, and the sensed signals obtained in the laboratory were compared under conditions of varying gas flows, movement and varying pauses between breaths. After local Ethics Committee approval, we recorded observations in six adult patients who were monitored in the postoperative recovery room for periods of 15–25 min while one of the authors (A.M.C.) observed the patients continuously during each evaluation period.

RESULTS

Ambient temperatures for the volunteer studies were in the range 18–24 °C. Figure 3A and B show samples of typical signals recorded in the laboratory environment. The amplitudes of retrieved signals were in the range 40–400 mV; figure 3A illustrates this breath-to-breath variability, underlining the importance of setting the gain to an adequate level. Figure 3C demonstrates that varying the oxygen flow rate had only a small effect on the signal.

Ambient temperatures for the clinical study were 23–24 °C. Three female and three male adult patients (ages 27–64 yr) were monitored in the postoperative recovery ward. Table I presents clinical details of these patients and the results obtained. There was a wide range of values of IET and *f*. There was a variability of signal amplitudes within the clinical setting (42–320 mV) similar to that observed in laboratory studies. Figure 3D shows a typical signal recorded in a patient and includes an episode of apnoea; apnoeic periods were recorded in two patients (maximum durations of 11 s and 23 s). Subsequently, we have tested the instrument on another 12 patients and have found similar signal patterns during episodes of airway obstruction and apnoea. Excessive movements involving displacement of the mask were noted to produce signal artefacts and false positive alarms.

DISCUSSION

Ventilation in spontaneously breathing patients is currently monitored by ward staff who record the ventilatory frequency at intermittent intervals.

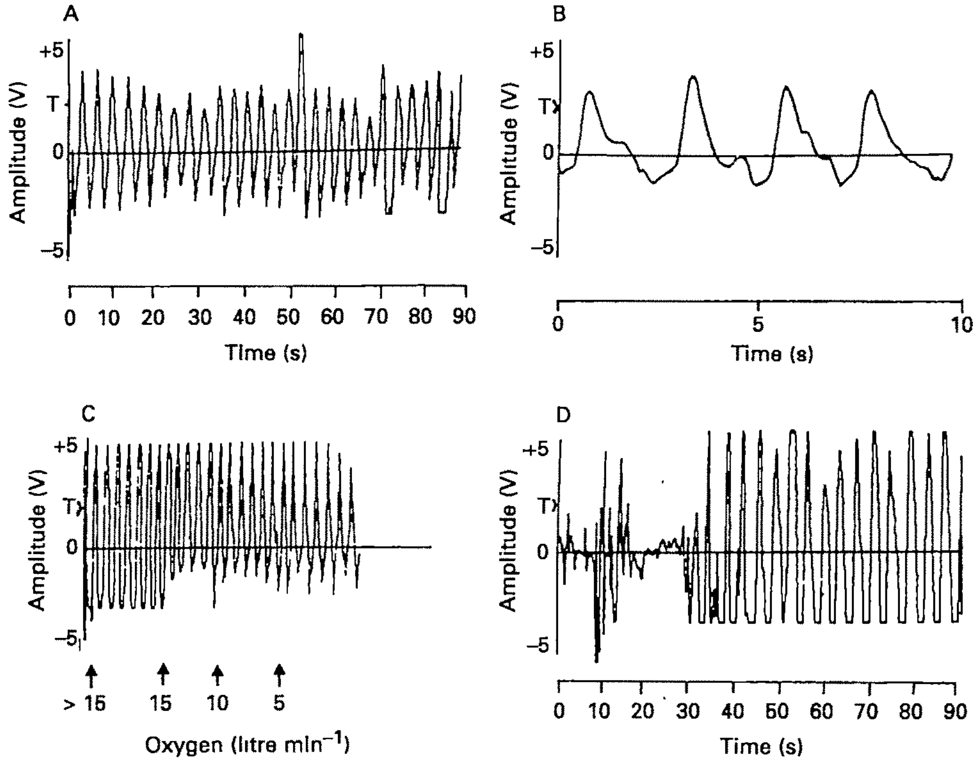

FIG. 3. Typical recordings in volunteers showing: varying signal amplitudes during spontaneous breathing over (A) a 90-s period and (B) a 10-s period; (C) the negligible effect of varying oxygen flow rates on the signal of interest; (D) apnoeic episode during a 90-s recording. T = Threshold voltage required for sensed signals to latch and trigger the counters of the AURA.

TABLE I. *Patient data and results. f = Ventilatory frequency; IET = interexpiratory time*

Subject No.	Age (yr)	Sex	Operation	Monitoring time (min)	*f* (b.p.m.) (max/min)	IET(s) (max/min)	Peak signal (mV) (max/min)	Apnoea (s)	False +ve	Comments
1	33	F	Pacemaker insertion	25	18/5	11/2	203/81	11	—	
2	41	F	Sigmoidoscopy + excision of polyp	20	17/13	7/2	196/108	—	—	Poor mask tolerance
3	27	M	Excision of pilonidal sinus	15	14/9	8/3	226/132	—	—	
4	64	F	Cervical lymph node biopsy	25	15/6	23/2	110/53	23	—	Movement artefact
5	48	M	Repair left inguinal hernia	22	36/17	3/1	226/42	—	—	
6	33	M	Repair of bilateral inguinal hernia	23	22/13	5/1	320/124	—	2+	Varying signal amplitude

Heavy demands on nursing staff makes continuous monitoring of ventilation in the spontaneously breathing patient an impossible ideal within the typical postoperative surgical or recovery ward setting. AURA is a novel non-invasive approach to monitoring spontaneous ventilation that has been found quick to prepare (less than 90 s), easy to use and unobtrusive. Nursing staff have commented favourably on the displays of ventilatory frequency, while the system's audio and visual alarms were helpful in the early identification of patients with intermittent airway or ventilation problems.

Signals were recorded despite patient movement, talking or coughing, the presence of a nasogastric tube, absence of dentition, or presence of an oropharyngeal airway. All visually noted apnoeic episodes that exceeded the IET alarm settings were detected. It was felt unlikely that these apnoeic episodes would have been noticed if the alarm had not been activated. Setting the gain control at too low a value led to false positive alarms.

Mask position was not found to be critically important, but it was necessary for it to overlie either mouth or nose, and preferably both. It was noted that less gain was required when the two sensors overlay the nares and lower lip or when an oropharyngeal airway was *in situ*. The incidence of signal artefact was low except during gross movements resulting in mask displacement. Alarms triggered in this instance acted as an indicator of patient compliance to their prescribed oxygen therapy. With the aid of a microprocessor-based evaluation technique, signal filtering, display of monitored variables and alarms are now being improved. We are also investigating the optimal number, size and configuration of sensors within the mask.

Observations of ventilatory frequency have been reported as an indicator of impending respiratory dysfunction [19]. AURA would be an appropriate respiratory transducer in those patients requiring oxygen therapy. We are currently assessing the system in a larger series of patients at risk of apnoea on the intensive care unit, the respiratory medicine ward, and post-operative surgery ward.

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A NEW OPTICAL TRANSDUCER FOR ARTERIAL PRESSURE MEASUREMENT

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SUMMARY

A new optical pressure transducer system (Viggo) has been assessed and compared with a standard P10 transducer (Spectramed) using a similar 20-gauge cannula, both in vitro *in terms of linearity and frequency response and* in vivo *using an animal model. The linearity of the transducers was comparable; the resonant frequencies were 106 Hz and 75 Hz, respectively. However, the resonant frequency of the complete Spectramed system including 150-cm tubing was 11 Hz. The frequencies at which the output amplitude error exceeded 10% of the initial amplitude for the Viggo and for P10 with and without 150-cm tubing were 32 Hz, 24 Hz and 4 Hz, respectively. The principal advantage of the new transducer is that it is sufficiently compact to be mounted directly in the cannula at the wrist, so obviating the use of connecting tubing between the transducer and the cannula.*

KEY WORDS

Arterial pressure measurement transducer. Measurement techniques. arterial pressure, intra-arterial.

The accuracy of clinical invasive arterial pressure monitoring is often compromised by the use of long lengths of connecting tubing, large volume transducer domes and a transmission liquid saturated with air. These factors greatly reduce the frequency at which resonance becomes significant. Appropriate damping devices may extend the range of accuracy, but are not used widely. A new disposable optical transducer (Viggo) is sufficiently compact to be mounted in the cannula hub, thus increasing the resonant frequency to a point at which accurate recording is possible even without measures to reduce the effects of resonance in the recorded signal.

Studies of the dynamic response of modern catheter–transducer systems have tended to omit the intravascular cannula from the system under test. Such studies are inapplicable to the clinical situation. In practice, a narrow gauge cannula is always used and this is one of the main sources of resistance, causing a substantial reduction in the sine wave frequency components of a signal at which errors become significant.

In this study, five prototypes of a new optical cannula–transducer system (Viggo, U.K.) were evaluated by laboratory methods and compared, *in vitro* and *in vivo*, with a conventional clinical strain gauge transducer, the P10 (Spectramed, U.K.) attached to a standard pressure monitoring kit (Spectramed, U.K.). Cannulae of similar diameter and length (4440-4, Viggo, U.K.) were used in both systems.

The optical transducer was compared with the Spectramed system in terms of linearity, frequency response and damping factor. The effect of the presence of manometer tubing on the Spectramed system was evaluated also.

MATERIALS AND METHODS

The transducer systems

Viggo group. Five were studied. The system contains a disposable element consisting of a 4440-4 20-gauge arterial cannula (Viggo, U.K.), the transducer and the fibreoptic connection to a preamplifier interface. The transducer consists of a reflective membrane 1 mm in diameter and three

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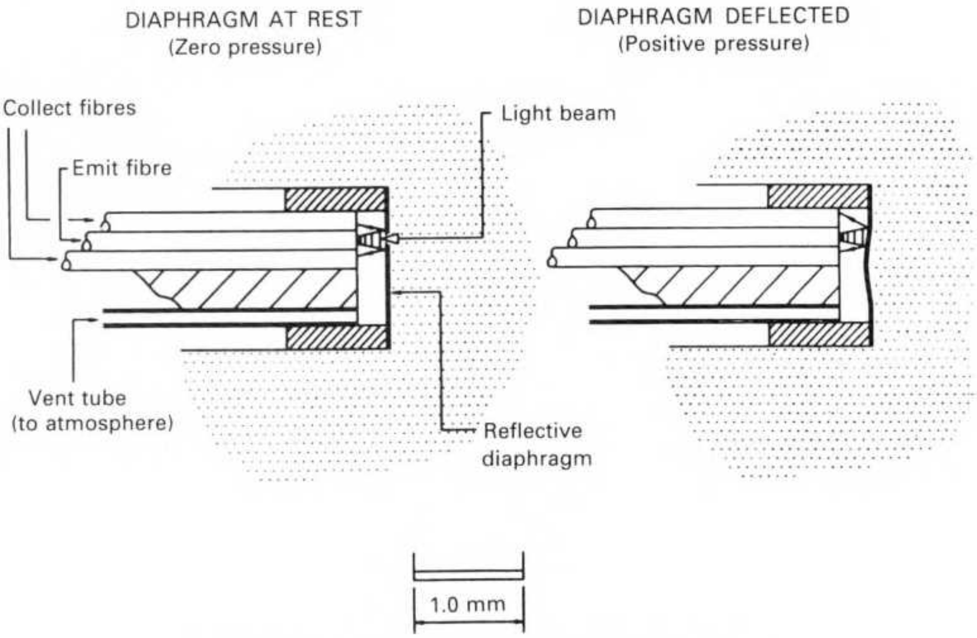

FIG. 1. Viggo transducer: optical fibres and diaphragm.

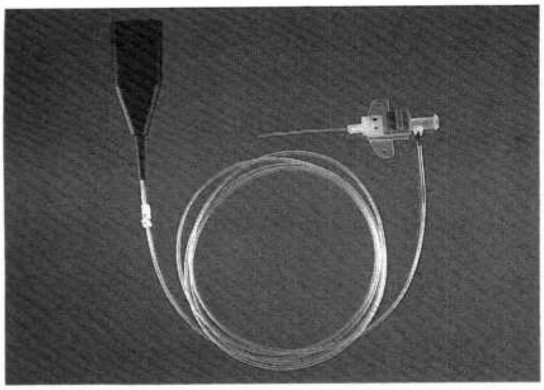

FIG. 2. The 20-gauge cannula, transducer, fibreoptic cable and preamplifier interface.

optical fibres mounted in a row a short distance from the membrane (figs 1, 2). The two outer fibres are linked to photodiodes mounted in the connector and the middle fibre terminates in the connector so as to receive a light input from the preamplifier interface. Application of pressure to the transducer deflects the light reflected from the centre fibre and hence alters the proportion of light received by the two outer fibres. The preamplifier interface is designed to connect to the transducer remotely via a fibreoptic cable. The power requirements of the Viggo preamplifier interface are designed to be run from any standard operating theatre monitor. The preamplifier also provides an oscilloscope output which was used for all measurements.

P10 group. Five were tested. Each comprises a P10 transducer (Spectramed, U.K.) and a standard disposable pressure monitoring kit (Spectramed, U.K.) consisting of a transducer dome with integral flush device, 150 cm of manometer tubing and a three-way tap. In all tests, the P10 transducer was connected to a 4440-4 (Viggo, U.K.) 20-gauge arterial cannula. The P10 transducer was tested in two forms, with and without manometer tubing. In this study, "Spectramed system" refers to the complete transducer system described above and "P10 transducer" refers to the transducer tested without flush device and manometer tubing. The space behind the dome membrane was flushed with saline to remove all visible bubbles before the transducer was fitted and the whole system was flushed repeatedly with saline until there was no further visible evidence of bubbles.

Laboratory test design. Each Viggo system was paired with a Spectramed system. Each system

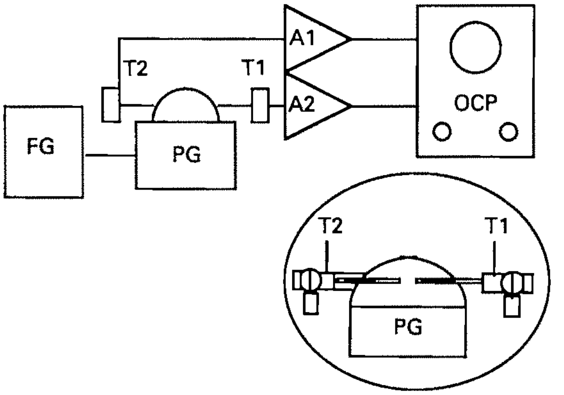

FIG. 3. Laboratory test design. FG = frequency generator; PG = pressure generator; OCP = oscilloscope; T1, T2 = transducers; A1, A2 = amplifiers.

was connected to one of two ports of the dome of the pressure generator. The diameter of the 20-gauge cannula was narrower than the port diameter of the dome and a rigid, saline-filled plastic extension tube was incorporated between the port and the hub of the cannula and sealed to ensure a good fit. The tip of the cannula was inside the chamber of the dome (fig. 3). Thus in both systems the same pressure was applied to the tip of the cannula and the presence of the extension tube was of no consequence to the measurement. Following assembly, the entire apparatus was flushed meticulously with saline to prevent retention of bubbles.

Linearity and reproducibility

Five Viggo optical and two P10 transducers were tested for linearity against a mercury manometer over the range 0–250 mm Hg. The preamplifiers used were the Viggo optical transducer interface for the Viggo system and the transducer preamplifier of a two-channel chart recorder (Lectromed Multitrace 2, Ormed Engineering U.K.) for the Spectramed system. The outputs of both preamplifiers were recorded on two channels of the chart recorder. This recorder was selected as it had been tested previously with a sine wave frequency generator and no evidence of resonance or fade was seen at frequencies less than 60 Hz. The chart recorder was considered, therefore, to have a response adequate for the studies.

Frequency response

The two types of transducer were compared by the pure sine wave method [1–3]. The sinusoidal pressure waveforms were produced by driving a Biotek 601A pressure transducer calibration unit (Bio-Tek Instruments Inc., Winooski, VT 05404, U.S.A.) with an electrical sine wave generated by a TG150DM transistor oscillator (Levell Electronics, U.K.). The Biotek 601A pressure transducer calibration unit is referred to as the pressure generator and the Levell TG150DM transistor oscillator is termed the frequency generator.

Testing of the pressure waveform generator. The sinusoidal pressure produced by the pressure generator and the frequency generator was tested against four different transducers: the Viggo optical, the P10, the disposable type TNF (Gould Medical, U.K.), and the Bell and Howell type 4-422-0001 (Devices Ltd., U.K.), connected in turn without cannula or tubing to a port of the pressure waveform generator. In the case of the Viggo optical transducer, this was detached from its cannula and sealed into a male Luer connector with epoxy resin so that the transducer membrane was flush with the tip of the fitting.

The sine frequency of the frequency generator was varied while keeping the amplitude constant. The frequency and amplitude of the outputs of the four transducers were measured using a two-channel digital oscilloscope (1602, Gould Medical, U.K.). At the same time the oscilloscope output was checked for possible deviation from a pure pressure sine wave by Fourier analysis.

The output signal showed an increase in amplitude at frequencies greater than 32 Hz, although resonance occurred at much greater frequencies for each of the four transducers—130 Hz for the Viggo optical, 125 Hz for the Spectramed P10, 100 Hz for the TNF Disposable and 120 Hz for the Bell and Howell transducer. This showed that the pressure generator itself was not resonating at a particular frequency and that the output signals were relevant to each of the transducer systems. However, the pressure generator itself may not give a constant amplitude at frequencies greater than 32 Hz in spite of a constant input amplitude, as the output amplitude increased with the increase in frequency. For this reason it was considered appropriate to apply a correction factor for frequencies greater than 32 Hz, using the ratio of the observed amplitude to the amplitude at 1.5 Hz (the initial amplitude) for subsequent tests with a cannula attached to the transducer.

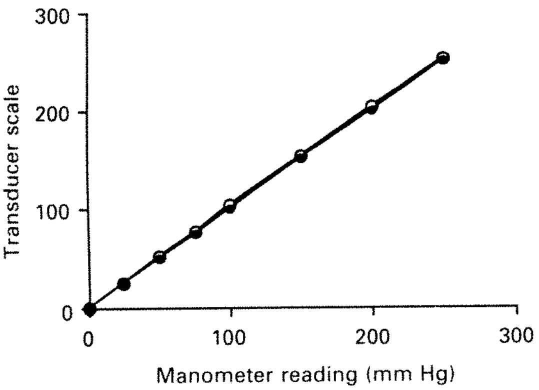

FIG. 4. Linearity testing of transducers. Comparison of output signals of Viggo (○) and P10 (●) against a mercury column.

Testing of the transducer systems. The paired systems were connected to the pressure generator as described above. The frequency was varied while keeping the amplitude constant and the displayed oscilloscope output was recorded.

In addition, the step-response of each system was measured and the undamped natural frequency and degree of damping calculated according to the method of Hansen and Warburg [4] using a 1.5-Hz pressure square wave generated by the pressure waveform generator. The amplitude of the first overshoot was not used for the subsequent calculations, to avoid errors arising from possible imperfections in the square wave.

Fourier analysis of arterial pressure signal

Two greyhound dogs (mean weight 24 kg) were used for arterial pressure signal analysis. The animals had been prepared for another study and were anaesthetized with thiopentone 20 mg kg^{-1}; anaesthesia was maintained with 1% α-chloralose 1 ml kg^{-1} h^{-1}.

A previously tested Viggo optical transducer with 20-gauge arterial cannula was used to cannulate the left femoral artery. The right femoral artery was cannulated with a similar 20-gauge arterial cannula, to which was attached a Spectramed system also tested previously. Both transducers were kept at the same level with reference to the heart.

The outputs from both transducer pre-amplifiers were connected both to the two-channel chart recorder and to a TM 7002 computer (Tandon, U.S.A.) running under MSDOS and a CED 1401 Data Acquisition System (Cambridge Electronic Devices, U.K.). Measurements of systolic, diastolic and pulse pressure were made from the chart recorder trace and Fourier analysis of pressure waveforms was performed by the CED 1401 controlled by the "Waterfall" programme (CED, U.K.). The accuracy of the Fourier analysis system was confirmed first by applying a pure sine wave from the frequency generator and comparing the displayed graph of amplitude against the sine wave frequency with an oscilloscope trace and, second, by repeating the comparison with a mixture of two pure sine waves.

RESULTS

Linearity

For both systems linearity over the range 0–250 mm Hg is presented in figure 4, which shows a near perfect co-relation with physical calibration against a mercury manometer.

Frequency response

Frequency response of pressure generator with bare transducers. The relative increase in the amplitude of the output signal with the increase in frequency and the resonant frequency at which the amplitudes were maximal varied considerably for the four transducers. The output signal amplitude remained constant up to 32 Hz, after which it increased with the increase in frequency. Therefore a correction factor was derived, as stated in the Methods section.

Frequency response of the transducer systems. The results of the Viggo optical and the Spectramed systems, the latter with clinically used manometer tubing, are presented in figure 5. The resonant frequencies of the cannula-mounted Viggo optical transducer and the P10 transducer attached directly to a cannula were 106 Hz and 75 Hz, respectively. Increases in amplitude gain of more than 10% were observed at approximately 32 Hz and 24 Hz, respectively. However, when the P10 transducer was attached to the cannula by 150 cm of standard Spectramed manometer tubing, greater than 10% increase in gain occurred at only 4 Hz and its resonant frequency was found to be only 11 Hz (fig. 5). The mean amplitude gain ratio with increase in the applied frequency, for five sets each of the cannula-mounted Viggo optical transducer and the Spectramed system with tubing, showed a gain of more than 10% (i.e. 10% error) at a significantly

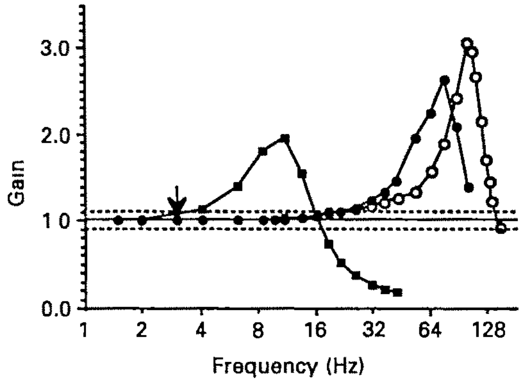

FIG. 5. Relationship between the gain of the measured output to the output at 1.5 Hz, and the sine frequency, in three transducer systems: Viggo optical transducer (○); Spectramed P10 (●); P10 with 150-cm tubing (■). Dashed lines represent 10% deviation from a gain of 1.0. Gain of P10 transducer with tubing exceeds 10% at 3 Hz (arrow).

greater frequency with the Viggo optical (32 Hz) than with the Spectramed (4 Hz). The degree of damping for both transducers without manometer tubing and Spectramed system with tubing was 0.16 (Viggo), 0.24 (P10) and 0.42 by the step-response method, and the resonant frequencies were similar to those obtained by the sine wave method.

Fourier analysis of the dog femoral artery waveform showed that more than 99% of the energy of the pressure waveform was contained in the frequencies up to the 10th harmonic (fig. 6). Even when the heart rate was 180 beat min^{-1} (i.e. a fundamental frequency of 3 Hz) no harmonic components were detectable at frequencies greater than the 10th harmonic (30 Hz) for both systems.

DISCUSSION

The results show good correlation between the two transducers in terms of linearity on static testing.

Testing of the frequency response in the clinical range was performed by the sine wave method because this method does not depend on a perfect theoretical single degree of freedom system for its interpretation [4, 5]. However, as the resonant frequency of the Viggo system was 106 Hz and as we were unable to show a flat response for the pressure waveform generator itself beyond 32 Hz when the four transducers were connected directly to the pressure generator chamber, the step-response method, rather than the measured amplitude at sine wave frequencies, was used to calculate the undamped natural frequency and degree of damping. The results of *in vitro* dynamic testing indicate that the presence of the saline-filled dome and tubing in the complete Spectramed system degraded its dynamic response by decreasing the resonant frequency from 75 Hz to 11 Hz and by decreasing the frequency at which 10% increase in gain occurred from 24 Hz to 3 Hz (fig. 5). Under such conditions, accurate recording of systolic and pulse pressures would not be likely. Fourier analysis of the pressure waveform in the

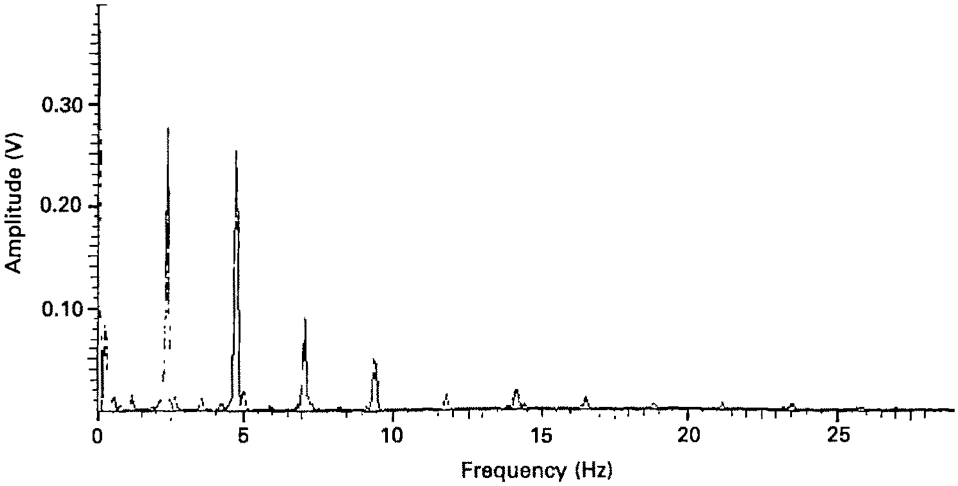

FIG. 6. Fourier analysis of dog femoral arterial pulse with Viggo transducer.

dog shows the importance of frequencies up to 20 Hz at a heart rate of 120 beat min^{-1}. Even in the resting animal with a heart rate of 120 beat min^{-1}, most of the energy is represented by frequencies greater than 4.5 Hz because resonance starts to occur. The Spectramed system would be expected to over-read by at least 20%.

The frequency response of clinical catheter–transducer systems has been reported for test apparatus which has not included a cannula [6, 7] or connecting tubing [8]. This grossly underestimates the resonance effects produced by the complete system in the routine clinical setting. Such effects are produced by the compliance of the transducer membrane, which should be small for a well-designed transducer, but are caused predominantly by the compliance of the tubing and the compressibility of the fluid and any bubbles it may contain. However much the system is flushed, there are always microscopic bubbles in the fluid unless this has first been de-gassed by boiling [1, 8–11]. This is probably impractical clinically. As a general rule, the larger the volume of the tubing, the less is the natural frequency of the system. In contrast, the narrower the tubing, the greater is the damping, and this also limits the frequency response [4, 5].

Adequate frequency characteristics of devices for measuring arterial pressure have been described by Gardner [6]. Based on comparisons with clinical recordings, Gardner suggested that an adequate dynamic response for all pressure waveforms was possible with a natural frequency as little as 13 Hz, provided damping was adjusted carefully. However, the Spectramed P10 system, which is one of the best known non-disposable systems, has a resonant frequency of only 11 Hz when connected with 150 cm of manometer tubing.

If optimal damping of the Spectramed system were achieved by the use of a suitable adjustable parallel-damping device [9] (whether a hydraulic device or its electronic equivalent) in conjunction with routine step-response testing to check adjustment, its response could be made adequate for clinical purposes unless the arterial waveform was unusually demanding. However, a fixed damping device may well not be satisfactory in practice, as there is great variation between individual systems and the amount of gas present in the system varies during use.

To eliminate these problems under all clinical circumstances, it is logical to remove the tubing and keep the transducer dome as small as possible. Unfortunately, the commonest site for the placement of an arterial cannula is the radial artery at the wrist. A bulky, rigid device attached to the cannula at this site is cumbersome and may cause kinking or even withdrawal of the cannula during unwarranted movement and even a short length of compliant and flexible connecting tubing, which is sometimes used to overcome the problem of fixation and movement, may nullify the potential improvement in frequency response.

The Viggo optical system uses a sensing element only 1.4 mm in diameter and 4 mm in length, mounted on a flexible fibreoptic cable. In its present form it is supplied mounted in the side of the slightly extended hub of a standard Viggo arterial cannula which incorporates a miniature tap. It is therefore practicable for use without even a short length of saline-filled tubing at the wrist. There is, nevertheless, a problem with mounting the transducer system at the wrist: the zero reference point changes with the level of the wrist. Therefore, it may be necessary to incorporate an offset adjustment on the pressure channel amplifier in which the user could enter the vertical distance between the transducer and mid heart level. Also, the highly undamped characteristics of the Viggo transducer may require some form of fixed damping device to improve further its dynamic performance.

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THE FIRST YEAR'S EXPERIENCE OF AN ACUTE PAIN SERVICE

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SUMMARY

The benefits, risks and resource implications of providing an Acute Pain Service were assessed during the first year of the service. Six hundred and sixty patients recovering from major surgery were treated with patient-controlled analgesia (510 patients) or extradural infusion analgesia (150 patients). The results of a prospective outcome study showed that pain control was good: more than 60% of patients scored their pain as mild during the first 24 h. Only 10% of patients complained of severe postoperative pain. Eight patients developed potentially serious complications including respiratory depression and hypotension; the diagnosis and management of these problems on general wards is discussed. Retrospective analysis of the incidence of postoperative chest infection in surgical patients showed a marked reduction during the first year of the service (1.3% in 1988, 0.4% in 1989–90 ($P < 0.01$)).

KEY WORDS

Pain: postoperative, acute pain service

"The treatment of pain after surgery in British Hospitals has been inadequate and has not advanced significantly for many years".

This opening statement from the Working Report [1] on Pain after Surgery of the Royal College of Surgeons and the College of Anaesthetists highlights the lack of progress in the provision of analgesia after major surgery.

The development of Acute Pain Services as described by Ready and colleagues [2] is an attempt to address this problem by the introduction of a multidisciplinary team to improve the management of acute pain throughout the hospital. The Acute Pain Service is responsible for the training of medical and nursing staff, organization of services to provide adequate levels of care, audit and evaluation of new and existing methods of treatment and undertaking clinical research into postoperative pain management.

Despite extensive experience in the U.S.A., there has been little development of Acute Pain Services in the U.K. because of manpower constraints [3] and recommendations have suggested that newer techniques should be restricted to High Dependency Units [4]. However, fewer than 30% of British Hospitals have a High Dependency Unit [5] and the restriction of complex methods of analgesia to these units would result in little improvement in the quality of pain relief for the majority of the surgical population.

It was decided, therefore, to evaluate outcome, including benefit, risks and resource implications, of providing an Acute Pain Service for general wards in a single site District General Hospital.

ACUTE PAIN SERVICE

The service which has been operating since April 1989 is based on the existing Obstetric Anaesthetic Service and is provided by three Consultant Anaesthetists, an Acute Pain Sister and the on-call obstetric anaesthetic junior staff. The service supervises the provision of acute pain relief throughout the surgical unit.

Methods of pain relief

Two standardized methods of pain relief are used:

Patient-controlled analgesia (*PCA*). A solution of morphine 50 mg in normal saline 50 ml was used in the PCA pumps. They were set to deliver a bolus dose of 1 mg with a lockout time of 5 min. No background infusions were used.

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Extradural infusion analgesia (*EIA*). A solution of 0.15% bupivacaine 50 ml with 5 mg of preservative-free diamorphine was infused at 4–8 ml h^{-1}. The dose of diamorphine was reduced to 2.5 mg/50 ml if the patient was older than 65 years of age.

Equipment

In the first year of the Acute Pain Service, the majority of patients receiving PCA were treated using Graseby PCAS pumps (Graseby Medical Ltd, Watford, Herts). Ten of these units were used. An additional three Bard PCA1 pumps (Bard Ltd, Crawley, W. Sussex) were used for the last 9 months. Extradural infusions were maintained using PCA pumps in the background infusion mode and Graseby MS2000 syringe drivers.

Criteria for admission to and discharge from the service

Any patient requiring opioid analgesia for the relief of postoperative pain or any acutely painful condition (e.g. pancreatitis or fractured ribs) was eligible for admission to the service. The analgesic techniques (PCA and EIA) were continued until the patient was comfortable or able to take oral analgesia.

Organization

These techniques were used by all members of the Anaesthetic Department (10 Consultants, nine Trainees and one Clinical Assistant) for patients undergoing major surgery. The method of analgesia was explained to the patient at the preoperative visit. When EIA was chosen, the extradural was sited where possible at the dermatomal midpoint of the proposed incision and used for peroperative analgesia. The postoperative treatment regimen was initiated by the nursing staff under the direct supervision of the anaesthetist in the recovery room immediately after surgery.

Before the introduction of the service to each ward, staff were given demonstrations of the equipment, and tutorials about the techniques and monitoring requirements were given by members of the Acute Pain Team. An explanatory document about the service and the techniques used was provided to each ward. In order to minimize the risks to patients nursed on general wards, several recommendations were made:

TABLE I. *Nursing pain scores*

Score 0 = No pain at rest
No pain on movement
Score 1 = No pain at rest
Slight pain on movement
Score 2 = Intermittent pain at rest
Moderate pain on movement
Score 3 = Continuous pain at rest
Severe pain on movement

(1) Patients were sent only to those wards where the Acute Pain Team deemed there were adequate numbers of trained staff.
(2) Standardized treatment regimens were used for both PCA and EIA.
(3) The introduction of written procedures and In-Service Training was the responsibility of the Acute Pain Sister.
(4) There was 24-h availability of a named anaesthetist with designated Consultant cover.
(5) Facility for continuous oximetry and transfer to ITU for high risk patients was available.
(6) Continuous oxygen therapy via nasal cannulae was administered to high risk patients for 2–3 days.

Nursing observations. Recovery staff recorded the patient's ventilatory frequency, pain score and, in the case of EIA, the dermatomal level of the block (tested by loss of temperature sensation) at 15-min intervals. On the patient's return to the ward, these observations were continued at 1-h intervals for the first 4 h and then 4-hourly if the patient's condition was satisfactory. Details of the volume of analgesic infused and the condition of the i.v. site were also recorded. The pain score (table I) was a simple nurse assessment of the patient's degree of pain at rest and on movement [Prys-Roberts, personal communication].

Ward rounds. Following referral to the Acute Pain Service, patients were assessed at regular ward rounds by the Acute Pain Team. During these visits at 24 h and 48 h after surgery, a record was made of the patient's assessment of pain (visual analogue score 0–10), the incidence of nausea and vomiting and degree of patient satisfaction with the technique. I.m. antiemetics were prescribed on an "as-required" basis.

Pain assessment. The nurse and patient scoring of pain were compared by grading each as mild,

TABLE II. *Gradation of pain scoring. Nurse score = first six 4-hourly scores; patient = VAS 0–10*

	Nurse	Patient
Mild	0–6	0–3
Moderate	7–12	4–6
Severe	13–18	7–10

moderate or severe (table II). The nurse score was obtained by summation of the first six 4-hourly pain scores on the ward. The patient score was a single VAS (0–10) at 24 h. All results were assessed using the unpaired *t* test, Welch's test or, for non-parametric data, chi-square test.

Retrospective study

The results of the regular Review of Nosocomial Infection in the Surgical Unit were analysed retrospectively. The diagnosis of lower respiratory tract infection was made by the Infection Control Officer on the basis of the Atlanta criteria [6] of fever, cough and purulent sputum.

Audit of workload

Audit of the working pattern of the Consultant and Trainee anaesthetists involved was undertaken over a 2-month period.

RESULTS

Patient data

The Acute Pain Service supervised 660 patients on 18 general wards in the first year (table III). PCA was used three times more frequently than EIA. The mean age of patients receiving PCA was significantly less than that of those having EIA, and male patients were significantly older than female patients ($P < 0.01$). The overall age range of patients was 12–92 yr. The mean duration of treatment was 55.5 h for both PCA and EIA (range 1–207 h). The PCA group received morphine 2–200 mg in the first 24 h. Female patients used significantly smaller doses of morphine than male patients in the first 24 h ($P < 0.005$) and the duration of their treatment was shorter ($P < 0.0001$).

TABLE III. *Patient details (mean (SD or range))*

	PCA		EIA	
	Female	Male	Female	Male
No. of patients	363	147	80	70
Age (yr)	48 (14–88)	59 (18–89)	56 (18–89)	65 (25–92)
Weight (kg)	65 (13)	73 (14)	65 (17)	72 (17)
Dose of opioid (mg/24 h)	43 (21)	49 (31)	9.5 (4)	9.5 (5)
Duration of treatment (h)	50 (1–144)	61 (4–190)	54 (9–207)	57 (3–168)

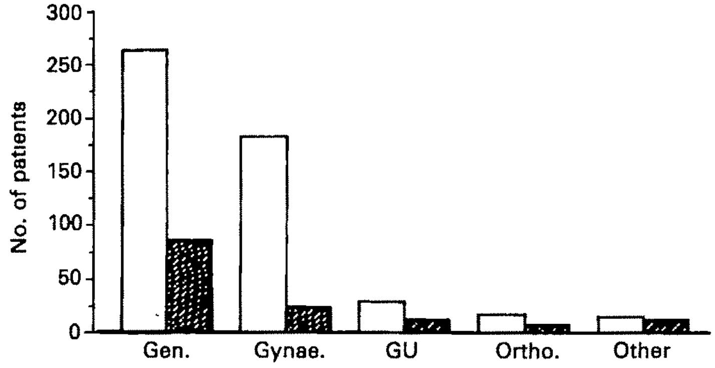

FIG. 1. Referral pattern. □ = PCA; ▨ = EIA. Gen. = General surgery; Gynae. = gynaecological surgery; GU = genito-urinary surgery; Ortho. = orthopaedic surgery.

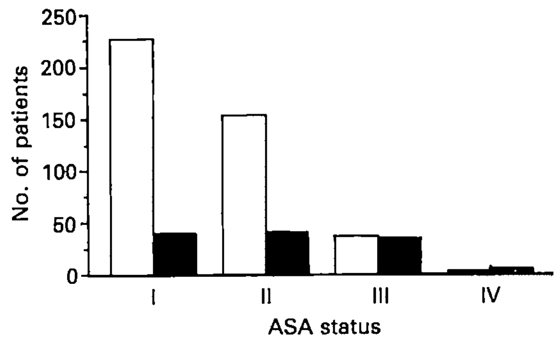

FIG. 2. ASA status and methods of analgesia. □ = PCA; ▨ = EIA.

TABLE IV. *Pain assessment and patient satisfaction*

	PCA		EIA	
	Patient	Nurse	Patient	Nurse
Pain assessment				
Mild (%)	63	73	77	85
Moderate (%)	26	17	16	10
Severe (%)	11	10	7	5
Satisfied (%)	96		91	

TABLE V. *Emetic sequelae (% or mean (SD))*

	PCA		EIA	
	Female	Male	Female	Male
Vomiting (%)	27	10	26	13
Nausea (%)	28	17	19	24
Dose of opioid (mg/24 h)	44 (20)	51 (30)	9.5 (4)	9.5 (4)

Referral pattern

The majority of patients were referred to the service after abdominal general or gynaecological surgery (fig. 1). Non-surgical referrals included patients with fractured ribs, acute back pain, pancreatitis and extra-amniotic termination of pregnancy.

Figure 2 illustrates the type of analgesia used and the ASA grading of patients: patients receiving PCA were more commonly ASA I or II, whereas a greater proportion of patients with EIA were ASA III or IV ($P < 0.01$).

Pain scores and patient satisfaction

Nursing and patient assessment of pain were broadly in agreement (table IV). The majority of patients experienced mild pain during the first 24 h, with only 7 % of patients receiving EIA and 11 % receiving PCA complaining of severe pain. The mean patient scores for the first 24 h were low for both treatment groups (mean VAS: PCA 3.5; EIA 2.2). Patients receiving EIA were more likely to have no pain or mild pain than those with PCA (chi-square, $P < 0.05$); however, a greater proportion of patients with PCA were satisfied with their method of analgesia (chi-square, $P < 0.05$).

Complications

Emetic sequelae were common with PCA and EIA (table V). Vomiting was twice as common in female patients compared with male patients and more frequent after gynaecological surgery (chi-square, $P < 0.01$). The incidence of nausea and vomiting was not related to the dose of opioid.

Urinary retention after EIA could not be assessed because the majority of patients receiving this form of analgesia routinely underwent catheterization.

Respiratory depression. The mean slowest ventilatory frequency recorded for both PCA and EIA was 15 b.p.m. (range 6–20 b.p.m.). Ten patients in the PCA group and three in the EIA group had ventilatory frequencies of less than 10 b.p.m., but had no other clinical evidence of respiratory depression. Four patients receiving PCA and one patient in the EIA group had airway obstruction associated with oversedation requiring the use of i.v. naloxone. Three of these patients had a ventilatory frequency less than 10 b.p.m., but the remaining two patients had frequencies in the normal range.

Hypotension secondary to relative hypovolaemia in the early postoperative period was a problem in the EIA group. The 8th thoracic dermatome was the mean maximum height of sensory block, (range T2–12). The mean smallest systolic arterial pressure with EIA was 100 mm Hg (range 60–140 mm Hg).

Prolonged unilateral motor block lasting 4–10 days and which delayed mobilization occurred in two patients recovering from lower abdominal surgery receiving EIA via a lumbar extradural catheter.

Incidence of lower respiratory tract infections. The review of the Noscomial Infection Surveillance showed that the incidence of lower respiratory tract infection in postoperative general surgical patients was significantly reduced in the first year of the Acute Pain Service (1.3 % of 4290 discharges in 1988; 0.4 % of 4667 in 1989–90 ($P < 0.01$)).

Audit of workload

Approximately 30 % of each Consultant session was spent on the ward rounds and work related to the provision of the service. The Trainee anaesthetist spent 26 % of his working time on acute pain work.

DISCUSSION

The major questions in the provision of Acute Pain Services relate to efficacy, safety and the use of limited resources.

Efficacy

The use of a single recording of the VAS at 24 h has been shown [7] to be a reasonable reflection of the patient's pain after surgery and correlates well in this study with the nurse scoring system used. Overall pain control in the two treatment groups was satisfactory, with more than 60 % of patients scoring their pain as mild during the first 24 h. The majority of patients treated were recovering from major abdominal surgery. Major orthopaedic and urology cases were referred less frequently as surgery tended to be performed under spinal anaesthesia, with postoperative non-steroidal anti-inflammatory analgesia.

Patients receiving i.m. analgesia were not studied, but two recent studies have highlighted the shortcomings of conventional i.m. analgesia. Kuhn and colleagues [8], in a study of a similar surgical population undergoing abdominal surgery, found that only 13 % of patients had little or no pain (mean VAS of all patients in the study during the first 24 h $\simeq$ 6.0). In a study of patient's expectations, Owen, McMillan and Rogowski [9] found that only 26 % of patients scored their pain as mild or absent.

A further measure of efficacy of analgesia is the patient's ability to cough well and co-operate with physiotherapy. Although these factors were not part of the prospective study, retrospective analysis of Microbiology records provided evidence that the incidence of chest infections decreased during the first year of the Acute Pain Service. Although a causal relationship cannot be established, there were no other major changes in caseload, antiobiotic therapy, surgical or ward practice to account for the reduction in chest infection.

EIA was used in a significantly older population with a higher incidence of pre-existing disease (ASA III–IV) undergoing more major surgery. This reflected our tendency to reserve the technique for high risk patients and those unable to use PCA. EIA was associated with good analgesia, with less than 7 % of patients experiencing severe postoperative pain. Although the level of patient satisfaction was high, it was less than in those receiving PCA, probably because of lack of patient control, reduced mobility, urinary retention and technical failures secondary to the siting of the catheter or equipment malfunction.

Safety

During the first year of the Acute Pain Service, eight of the 660 patients treated (1.2 %) developed potentially serious complications. Of the 510 patients receiving PCA, four patients had respiratory depression which required treatment with i.v. naloxone. Two of these patients had received concomitant analgesic therapy (opioid or NSAID) and two poorly selected elderly patients were too sleepy to use the device and received nurse-controlled analgesia. Three of the four problem patients occurred in the first 100 PCA patients and only one patient in the subsequent 450 patients gave cause for concern.

In the EIA group of patients (150), only one developed ventilatory problems, which were secondary to excessive sedation, airway obstruction and hypovolaemia. Two patients with lumbar extradural catheters complained of prolonged weakness of one leg, resulting in marked reduction in mobility. One of these patients developed deep venous thrombosis, despite the continuous extradural infusion of local anaesthetic.

The major concern in the extradural group was development of relative hypovolaemia 4–16 h after operation, secondary to inadequate fluid replacement and the sympathetic block caused by extradural bupivacaine. In one 70-yr-old male recovering from an abdomino-perineal resection, postoperative haemorrhage was inadequately treated as the hypotension was attributed incorrectly to the effects of the extradural block. The patient subsequently suffered a myocardial infarction and died. The incidence of hypotension decreased as anaesthetic and surgical staff became aware of this problem and paid particular attention to postoperative fluid replacement and the use of colloid solution with a longer half-life.

In addition, experience from the first 200 patients confirmed Ready's observation that over-sedation is a valuable clinical sign of impending respiratory depression. A simple sedation score has now been added to the routine postoperative observations.

Resource implications

Staffing. The Acute Pain Service as described, based on the existing obstetric anaesthetic services, did not involve additional staff other than the key appointment of an Acute Pain Sister. However, in a multiple-site District General Hospital or in an obstetric unit without adequate Consultant cover, additional sessions would have to be made available. The extent of the sessional commitment would obviously depend on the size of the service and the number of patients treated. A substantial part of the time spent by the Trainee anaesthetist was refilling and attending to problems with the PCA pumps. This proportion should decrease with the increasing involvement of the nursing staff, as a consequence of the inclusion of refilling PCA pumps in the extended role of the nurse.

Equipment. The PCA pumps proved to be robust and reliable [10]. The major complaint of nurses, surgeons and anaesthetists about the pumps was their lack of availability. The number of pumps was increased from six to 15 in the first year. At approximately £2000 each they are expensive, but their cost can be offset against reduced nursing time checking i.m. analgesia and the reduced cost of treating fewer chest infections.

Initially, EIA was provided by using the standard PCA pump in the background infusion mode. This pump required refilling twice a day and there is the potential for confusion between patients receiving PCA and EIA. To minimize this risk, EIA is now provided using an ambulatory PCA device (Bard Ltd) which uses a 250-ml infusion bag. These bags are prepared by pharmacy and usually provide analgesia for a little more than 2 days without refilling.

Support services. It was apparent from the outset of the service that refilling 10–15 pumps in a variety of surgical locations in a safe manner posed major problems. The use of standardized regimens for PCA and EIA and the active involvement of the Pharmacy Department resulted in the batch preparation of 50-ml syringes which are frozen and stored in the pharmacy. Supplies of these syringes and the 250-ml infusion bags for EIA are stocked in the recovery area for starting patient treatment. Ward staff automatically order a prefilled syringe or bag when a patient returns to the ward with a PCA or EIA pump.

Similarly, the involvement of the physiotherapy staff has increased during the development of the service. Physiotherapists now join the ward round and their assessment of the adequacy of analgesia and the patient's ability to cough is extremely valuable. In addition, they act as a source of secondary referrals to the Acute Pain Service when they encounter a postoperative patient with conventional analgesia who is unable to co-operate with physiotherapy.

CONCLUSION

The experience of the first year of an Acute Pain Service has demonstrated that the adoption of a multidisciplinary team approach may lead to a marked improvement in postoperative pain relief. Although attention has tended to focus on the patients receiving relatively sophisticated methods of analgesia, the change in attitude of surgeons, anaesthetists and nursing staff involved with the service has resulted in more attention being paid to all patients recovering from surgery. This has been demonstrated by the increased use of regional techniques in theatre, the use of i.v. opioids by recovery staff and the use of NSAID in the perioperative period. Regular ward rounds have been accepted readily as a major improvement over previous *ad hoc* arrangements and this daily audit of the service and feedback to anaesthetic and surgical colleagues has led to the delivery of a more consistent standard of post-operative care.

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CORRESPONDENCE

ANAESTHETIC EQUIPMENT FOR A DEVELOPING COUNTRY

Sir,—Pedersen and Nyrop describe their solution to the problem of anaesthetic delivery in underdeveloped countries [1]. Unfortunately, the design aims did not specifically address patient safety, and the machine appears to be based on the assumption that nitrous oxide must be made available.

Nitrous oxide is not an essential component of modern anaesthesia and should probably be avoided in countries where the cylinder supply and delivery apparatus are unreliable [2] and where continuous measurement of $F\mathrm{I}_{\mathrm{O}_2}$ is impractical. Simple drawover air techniques are extremely safe and will provide satisfactory conditions of anaesthesia for all surgery. If it is accepted that such techniques should be used in the peripheral district hospitals, then it is imperative also to promote their use in the central training establishment.

If nitrous oxide is unnecessary, the "machine" component of Pedersen and Nyrop's figure 1 becomes redundant. The oxygen concentrator can be connected directly to the drawover system so that figure 3 resembles the Tri-Service Anaesthetic Apparatus layout [3], a system with considerable saving and additional patient safety.

A previously-published account of the Malawi Anaesthetic machine [4] is not referred to, yet this describes several serious clinical problems which should surely have been identified and corrected by extensive clinical trials.

Finally, the Manley ventilator recommended [1, 4], must be one of the most unsuitable machines available, as it is extremely extravagant with anaesthetic gases. A simple electrically-driven ventilator would seem to be a more appropriate option.

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Sir,—I am sorry that Commander Tighe received the impression that our project did not specifically address patient safety, and that nitrous oxide must be available. The equipment was designed specifically to address patient safety: mortality rate at the hospitals has decreased approximately 20% since the new equipment was introduced (Information from Ministry of Health, Malawi). I agree that nitrous oxide is not an essential component of modern anaesthesia and the unreliable cylinder supply was one of the reasons for initiating this project. The machine will, indeed, operate without nitrous oxide.

The local staff preferred to use a Boyle anaesthetic machine and we decided, therefore, to design a machine to combine a drawover and a continuous flow technique. Several district hospitals have used the vaporizer alone, connected directly to the oxygen concentrator, and I have included a drawover technique in training anaesthetic staff. I do not agree that a simple drawover technique will provide satisfactory conditions of anaesthesia for *all* surgery, but it will provide satisfactory conditions for most surgery performed. Since the introduction of the Malawi anaesthetic equipment, the use of nitrous oxide has decreased both at District and Central level.

In his article, Fenton described his experiences using his modifications [1]. Problems arise, however, using a drawover vaporizer in the presence of positive pressure, especially if the screws are tightened at the overpressure valve [2]. Also, the importance of draining the oxygen concentrator of water has been emphasized by Carter [3].

The equipment was tested in Denmark by extensive clinical trials before delivery, and none of the problems described by Dr Fenton was identified. One reason for this could be that unmodified equipment was used. We bypassed the air outlet because we use air, not oxygen, to power the ventilator; the oxygen concentration decreases significantly if oxygen is used. The same costs arise using either 2 or 25 litre min^{-1} of air/oxygen, and the oxygen concentrator uses 400 $\mathrm{W\,h}^{-1}$ independent of flow rate.

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SPINAL NEEDLES

Sir,—We read with interest the letter by Carrie and Collins [1]. We agree that wider bore pencil-point spinal needles may resolve both the technical difficulties of the 29-gauge and the greater incidence of post-dural puncture headache (PDPH) seen with bevelled 25- and 26-gauge types. To our mind, the technical difficulties of the 29-gauge needle are lack of feel in needle placement (although this may be overcome with experience) and the long delay for CSF to appear at the hub, usually more than 30 s when the patient is in the lateral position. There is also the risk of needle displacement at injection, which may account for the high failure rate [2, 3]. These are distinct disadvantages in both obstetric emergency anaesthesia and busy day-case surgical lists.

There is a much-reduced incidence of PDPH with the pencil-point needle compared with similar sized bevelled types [4]. Commonly used pencil-point needles include the Sprotte and Whitacre. We have undertaken a study of the use of the 25-gauge Whitacre needle (Vygon, Ecouen, France) in subjects aged less than 40 yr. In more that 40 patients undergoing short stay procedures with early mobilization, we have had no incidence to date of either backache or PDPH. The 20-gauge introducer provided with this needle makes it technically easy to use, feel is superior and CSF appears at the opaque hub in approximately 2 s in patients in the lateral position. We have had no unsuccessful blocks to date.

We have had three PDPH related to the use of the 29-gauge bevelled needle over the past 6 months. One came on after 48 h and required an extradural blood patch. We concur with other authors that blocks with this type of needle are not as reliable as those with larger bore needles.

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OPIOID RECEPTORS—THE ROLE OF THE SIGMA RECEPTOR?

Sir,—I read with interest the recent review by Pleuvry on opioid receptors and their ligands [1] and should like to add some comments concerning the sigma receptor.

Much confusion has surrounded the classification of this receptor. This arose from the fact that the racemic mixture of SKF 10047 (($\pm$)-N-allylnormetazocine; NANM) initially was used in binding and behavioural studies. Subsequently, it was found that, whereas ($-$)-^{3}H-NANM displayed affinity for classical opioid receptors (its binding was naloxone-sensitive), (+)-^{3}H-NANM bound to two separate, naloxone-insensitive sites in the mammalian central nervous system [2]. Binding of (+)-^{3}H-NANM to the first of these sites, termed the high-affinity site, was potently inhibited by compounds such as haloperidol and (+)-pentazocine and less potently by phencyclidine (PCP) and related compounds, and it is this site which is now referred to as the sigma receptor. The second site, termed the low-affinity site, displayed a drug specificity which was the same as that described previously for the PCP receptor, in that binding of (+)-^{3}H-NANM to this site was potently inhibited by PCP and related compounds such as ketamine. The PCP receptor exists within the N-methyl-D-aspartate (NMDA) receptor-operated ionophore and thus PCP receptor ligands act as non-competitive antagonists of the excitatory actions of NMDA [3].

It has been suggested recently that the sigma receptor may be identical to a high-affinity site labelled with ^{3}H-dextromethorphan (DXM) and that it may be this site which mediates the anticonvulsant and neuroprotective effects of sigma and DXM receptor ligands [4]. However, DXM itself, in common with many sigma ligands, has some affinity for the PCP receptor and has been shown to be an NMDA antagonist, both *in vivo* and *in vitro* [5]. Given the proposed importance of NMDA receptor-mediated events in the pathophysiology of both convulsive phenomena and neuronal death following ischaemia/hypoxia of the central nervous system [3], it seems likely that at least some of the therapeutically-useful actions of DXM may reflect functional NMDA antagonism at the PCP receptor rather than at the sigma site. Nevertheless, it is apparent that the potency of DXM cannot be accounted for solely on the basis of NMDA antagonism [5] and evidence suggests the possibility that DXM receptor ligands can act as antagonists at voltage-gated neuronal Ca^{2+} channels [6, 7]. It is not known if this property is also shared by classical sigma receptor ligands, but in the case of DXM itself, the combination of reduced Ca^{2+} influx through both voltage-gated Ca^{2+} channels and NMDA receptor-operated channels at the same concentration may account for its potent anticonvulsant and neuroprotective actions.

Finally, as stated by Pleuvry, it is as yet unclear which of the binding sites (the sigma site or the PCP site) might mediate the psychotomimetic actions of PCP-like drugs. This uncertainty is caused largely by the fact that many compounds, including PCP, show affinity for both receptors. Nevertheless, despite the fact that a number of established antipsychotics show a higher affinity for the sigma receptor than for the PCP receptor, most evidence at present suggests it is activity at the PCP receptor (and consequent NMDA antagonism) which underlies psychotomimetic activity. Thus, for a representative sample of drugs, the rank order potency for eliciting psychotomimetic activity in humans is PCP > ($-$)-α-cyclazocine > (+)-α-cyclazocine > ketamine > ($-$)-pentazocine > (+)-pentazocine, which is the same as that for affinity for the PCP receptor and NMDA antagonism, but the opposite of that for affinity for the sigma site [8].

Thus, despite the huge amount of work concerning the identification and pharmacological description of the sigma site, it remains to a large extent a binding site without a documented physiological role.

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DETERMINANTS OF ANTAGONISM OF NON-DEPOLARIZING NEUROMUSCULAR BLOCK

Sir,—The study by Beemer and colleagues [1] provides interesting information on the differences between agents, at different levels of neuromuscular block with different non-depolarizing neuromuscular blockers. Unfortunately, they ignore the effect of potentiation of this block in most of their subjects by the action of volatile anaesthetics, which would not be present in those patients receiving maintenance of anaesthesia by i.v. agents. Neither the anaesthetic drugs, nor the concentrations at which they were used are named in this study. It may be significant that the group with the fastest time for antagonism had the greatest rate of total i.v. anaesthesia (40%, 10/25) and so less potentiation of block. This is significantly different from an average i.v. maintenance rate of 14.8% (26/175) for all other patients (chi-square test corrected for continuity = 7.743 ($P < 0.01$)).

In their discussion, the authors note a clinically significant difference in time for antagonism from profound levels of block comparing alcuronium and atracurium. These groups differ significantly in the use of i.v. anaesthesia (alcuronium 7 *vs* 93; atracurium 29 *vs* 71; chi-square = 14.94 ($P < 0.001$)).

In the presence of this significant but unmeasured drug interaction, the results of this study may be suspect.

J. R. Campbell
London

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Sir,—Thank you for the opportunity to reply to the letter from Dr Campbell. We are aware of the fact that volatile anaesthetic agents may attenuate the effects of anticholinesterases in antagonizing competitive neuromuscular block. This is independent of their potentiation of the neuromuscular block and has been attributed to their effect on decreasing the rate of spontaneous recovery of the neuromuscular blocking agent [1]. Our results would support this conclusion when deep neuromuscular block is being antagonized.

In our study the incidence of usage of volatile and i.v. anaesthetic agents differed between the atracurium and alcuronium groups, although not between the individual anticholinesterase groups for each neuromuscular blocking agent.The more frequent use of volatile agents with alcuronium may have resulted in prolongation of the time for antagonism of deep neuromuscular block for alcuronium relative to atracurium. This was unlikely to have been the chief reason for the marked difference we observed, as we did not detect any difference in the times for antagonism of anaesthetic agents. However, to exclude this possible confounding effect, we did not compare directly the differences in reversal times between alcuronium and atracurium, as was shown clearly in table III. We did comment upon this large difference as it is a common finding [2] and, most importantly, it can now be explained readily by our observation of the role of spontaneous recovery of the neuromuscular blocking agent in antagonism of deep block.

The chief finding of our study, that of a bi-exponential relationship between the degree of neuromuscular block and the time for antagonism, cannot be obviated by the difference in usage of anaesthetic agents.

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TOXICITY AND PHARMACOKINETICS OF MORPHINE AND MORPHINE-6-GLUCURONIDE

Sir,—I was interested to read the paper by Hanna and colleagues [1], but feel that more information about the toxicity would have been helpful.

We are told that adverse reactions were assessed by direct questioning, but are not given any clue as to the methodology. Presumably, no assessments were made by the subjects themselves using such well validated methods as visual analogue and other rating scales. The subjective side effects need quantifying; the fact that all subjects suffered sedation after i.v. morphine compared with, for example, four of six after the administration of morphine-6-glucuronide 30 $\mu g\ kg^{-1}$ is difficult to put into perspective, since it is the degree of sedation that is important.

The same argument applies to the other recorded toxicities. The high incidence of an unusual side effect, namely that of a rash after morphine administration, is noteworthy and it might have been appropriate for the authors to describe the appearance, distribution and duration of the rash, factors of which we remain ignorant, and perhaps to speculate on possible causes of this toxicity.

We, too, are investigating the possible clinical applications of morphine-6-glucuronide and also have found it to be significantly less toxic than equivalent doses of morphine.

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London

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Sir,—I read with interest the paper on the pharmacokinetics of morphine and morphine-6-glucuronide in normal volunteers from Hanna and colleagues [1]. We also are studying the pharmacokinetics of morphine and morphine-6-glucuronide and I was surprised, therefore, in comparing these published data with our own that there were very large discrepancies between certain pharmacokinetic parameters, namely maximum plasma concentration (*Cmax*), area under the concentration–time curve (AUC) and plasma clearance (*Cl*). This, I am afraid, is caused entirely by incorrect units being assigned to these parameters in table I of the publication. The units of plasma concentration which appear in figure 1 as ng ml^{-1} are given as ng $litre^{-1}$ in the table without correction of the data. This error is then carried over into the calculated AUC which appears as ng h $litre^{-1}$, but which should be ng ml h^{-1}. Similarly, the volume unit for clearance, given as litre, should be ml, but additionally the computer program used divides the clearance by 60 to give the computed result in units of volume per minute; hence the actual units for clearance should be ml min^{-1}. Having established the correct units, these pharmacokinetic parameters show good agreement with out own and other published values. As comparison of published results amongst workers in the same field is commonplace it is imperative that these errors in units do not occur.

S. P. Joel
London

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1. Hanna MH, Peat SJ, Knibb AA, Fung C. Disposition of morphine-6-glucuronide and morphine in healthy volunteers. *British Journal of Anaesthesia* 1991; **66**: 103–107.

Sir,—We thank Dr Davis and Mr Joel for their interest in this work and are grateful for the opportunity to reply.

The methodology used for the side effect assessment was by direct questioning of the subject, with "yes" or "no" answers. Questions were asked at each blood sampling time, and the numbers of subjects responding positively to a question at any time during the study are reported in table II. Our subjects were also asked to report the time at which they felt completely normal (i.e. felt that they could think, move and eat normally).

We thoroughly agree that accurate assessment of the degree of a subjective side effect (and its duration) is important, but feel that this is better done in a more clinical context and in relation to analgesic potency. Our assessment as it stands is of limited significance; nontheless, the difference between morphine and M6G was quite striking.

The rash we observed following i.v. morphine sulphate was a typical urticarial response, spreading from the injection site up one arm. It was fully resolved within 1 h, and was associated with local itching This is a common documented side effect of i.v. administered morphine [1], and is almost certainly secondary to local histamine release. Indeed, morphine-induced skin weals have even been suggested as a model for the evaluation of histamine release inhibitors [2].

Simon Joel is quite right in pointing out our oversight in the presentation of the kinetic data. We trust this can be corrected, and thank him for his astute observation. The units in table I should read as follows: *Cmax* (ng ml^{-1}), AUC (ng h ml^{-1}), *Cl* (ml min^{-1}).

With regard to the relative toxicity of morphine and M6G, the information that Dr Davis has shown M6G to be less toxic is very much in line with out own studies of the respiratory effects of the two compounds [3] and we await publication of toxicity data from the Homerton group with considerable interest.

M. H. Hanna
London

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British Journal of Anaesthesia 1991; **67**: 364–365

BOOK REVIEWS

Anaesthesia, 3rd Edn. Edited by R. G. Miller. Published by Churchill Livingstone, Edinburgh. Pp. 2420; indexed; illustrated. Price £115.00.

This standard American textbook has been overhauled completely and is now in its 3rd edition. It consists of 2420 pages in two very large volumes, with an index of 115 pages.

Responding to trends in anaesthetic practice, the editor has placed more emphasis in this edition on i.v. anaesthesia, monitoring and the anaesthetic sub-specialties. New chapters include i.v. and inhaled anaesthetic delivery systems, many chapters on monitoring, and anaesthesia for orthopaedics, paediatric cardiac surgery and hypobaric medicine. The sections on regional anaesthesia and postoperative pain have been expanded.

The editor's approach to the problem of overlap of chapter contents is to allow each author a complete run at the subject, not interfering if repetition occurs, and then providing an extensive cross referencing system. This approach has its advantages, but must have added considerably to the bulk of the book.

Each chapter was edited by one of five consulting editors and the senior editor. This is described as a review that "equals or exceeds that of the most peer reviewed journals". It is to be hoped that this is a process which all chapters in major text books undergo and is not specific to this particular book.

The practice of anaesthesia in the U.S.A. is described extremely well, but there has been little attempt to seek the views of experts outside the U.S.A. There are more than 90 authors and only three who work in other parts of the world (Zimbabwe, Copenhagen and Melbourne) have contributed. This is a pity and weakens the book's international appeal.

However, Miller's *Anaesthesia* is well recognized as an excellent text book and the new 3rd edition is even better.

D. J. Rowbotham

A Colour Atlas of Dental Analgesia and Sedation. By G. J. Roberts and N. L. Rosenbaum. Published by Wolfe Publishing Ltd, London. Pp. 208; indexed; illustrated.

This book is an account of personal techniques of analgesia and sedation which have proved successful in the hands of the authors, and is directed to the needs of dental under- and postgraduates. The conjunction of local analgesia and sedation is not so surprising as might first be thought, as impeccable local technique is mandatory when treating apprehensive dental patients under sedation.

As the title implies, the book is illustrated profusely and the diagrams and photographs are of uniformly high quality.

The section on local analgesia is not as comprehensive as a single text, but is easily understood. The pharmacology of the local analgesic drugs is condensed and would not serve the needs of an anaesthetist. The sections on the use of nitrous oxide to allay anxiety and the use of i.v. sedation are disappointing. Regrettably, the text abounds in errors. So are minimal, for example "bodock" seal for Bodok, "Yanke for Yankauer; others are confusing, such as "Like oth opiates, benzodiazepines..." and some are dangerous, as wi the advocacy of methoxamine for the treatment of hype tension. The supine position is confused with the later recovery position.

There is a certain amount of confusion in the text, wit Guedel's stages of ether anaesthesia being equated with stage of analgesia and, despite the authors' acknowledged interchangeable use of inhalation psychosedation, oxygen–nitrous oxide sedation, relative analgesia and inhalation psychosedation in the text, they then proceed to differentiate between them. I.v. sedation is dealt with in some detail, but undue prominence is given to the use of flumazenil, which cannot be considered as part of routine care. It is surprising that, in a book intended to be practical, it is never suggested that when venepuncture is attempted, the bevel of the needle should be uppermost.

Needless repetition is an irritation to the reader and anecdotal accounts of patient care inappropriate in a textbook The layout is successful in placing most of the illustrations close to the relevant commentary, but this results in some difficulty in following the text. This book would be confusing to the trainee in anaesthesia and a disappointment to consultants in anaesthesia who have an interest in dental practice.

D. P. Braid

ECG Essentials—A Pocket Reference for Systematic Interpretation. By K. R. Murphy and J. J. Pelton. Published by Quintessence Publishing Co., Inc., Chicago. Pp. 176; indexed; illustrated. Price £17 50.

This pocket sized manual is a very useful addition to the large number of texts that are available detailing the basics of ECG interpretation In their preface, the authors suggest that their book represents a "happy medium" between the students' self-study manuals and the more complex larger text books of ECG interpretation. Certainly, this pocket manual provides extensive coverage of the wide variety of ECG abnormalities presented in an easily assimilated semi self-instruction format. Each section is written concisely and clearly, with excellent diagrams throughout. The use of quick diagnosis "boxed" sections within each chapter is very helpful, identifying the salient features of particular ECG abnormalities. Also worthy of special mention are the chapters on evaluating ECG axis, cardiac anatomy and screening for ischaemia and infarction, all of which are often particularly problematical for the uninitiated.

Readers with only a limited knowledge of ECG interpretation will be able to progress very quickly through basic principles to more complex analysis. In addition, more advanced students will be able to dip into the book at various points, using each chapter with its associated review questions as a separate learning experience or a revision exercise.

The text is well indexed and the ring binding makes the book very easy to use as a pocket manual. My only criticism is that I felt the appendices dealing with the ACLS procedures were possibly redundant and could have been omitted.

Overall, this little book is recommended as easily readable and a very useful guide to the essentials of ECG analysis.

D. B. Barnett

The Anaesthetic Plan: From Physiologic Principles to Clinical Strategies. By S. Muravchick. Published (1991) by Mosby Year Book, St Louis. Pp. 425; indexed; illustrated. Price £32.00.

The author of this brave book compares it with the standard, comprehensive textbooks of anaesthesia as a "blueprint to a completed edifice". His stimulus to write was that "many fundamental physiologic mechanisms and pharmacologic relationships are not adequately described in standard textbooks". So far, so good: but while Dr Muravchick undoubtedly has the breadth of understanding to teach effectively on a wide range of subjects, 400 pages is simply too restrictive.

There are two general chapters, then eight chapters based on physiological systems, and a final chapter dealing with risk and the role of the consultant. Each chapter starts with a generalization, works from principles to practice, and ends with a summary that perhaps should head the chapter. There are simple diagrams, but many of the flow charts are not easy to follow, in part because they were obviously produced on a computer with low resolution graphics. The chapters are well referenced, particularly to review articles, although there is a heavy bias to the American anaesthesia journals—particularly *Anesthesiology*. Surprisingly, Hedenstierna's work on the relation between atelectasis and virtual shunting is not mentioned.

The index is a little idiosyncratic ("Quiet tidal breathing" is indexed) and has slipped forward by two pages around the middle of the book. The book is pleasantly easy to read except for an abundance of unnecessary abbreviations, including MAC for "monitored anesthesia care", and a tendency to occasional obscure words such as orthostasis, heterometric, xenobiotics and diaphoresis. An editor might also have removed some of the ubiquitous *howevers*.

Ultimately, the book fails for two important reasons. First, the idea of an anaesthetic plan only works when there is a sound physiological basis for our actions but, as Dr Muravchick writes, "the complexity of disease processes and the virtually infinite variety of physiologic states simply make some things unknowable at the time the anesthetic plan is designed."

The second reason for failure is that, while not intended to be a comprehensive textbook, it ends up by covering too much too inconsistently. There is a curious mixture of deep thought and the self-evidently superficial. Acid–base balance is dealt with in half a page, the same amount of space given to congenital thrombocytopathy. Renal countercurrent mechanisms are not explained at all. Yet there are two pages of description of simple feedback control of arterial pressure, and it is felt necessary to remind readers that the primary function of the lung is gas exchange.

There is a good book lurking in *The Anesthetic Plan.* It is worth a read by candidates for examinations because it should make them think and because it is a good source of review references, even if they are mostly American. I hope it goes to a second edition, for which Dr Muravchick can decide which principles really are worth pursuing and which worth leaving aside until our understanding is more complete.

N. W. Goodman

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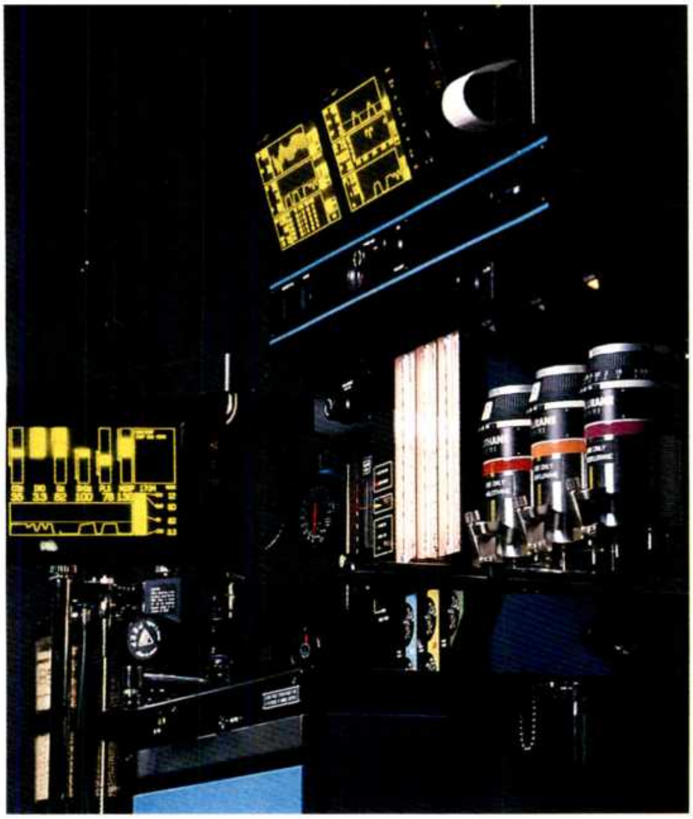

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